NEUROMAGNETIC LOCALIZATION OF CURRENT DIPOLE SOURCES IN COMPLEX PARTIAL EPILEPSY

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ABSTRACT

Magnetoencephalography (MEG) is a non-invasive imaging technique which measures the magnetic fields associated with synchronous electrical activity of the brain. Such synchronization may be produced experimentally, for example by sensory stimulation, but also occurs naturally in cases of epilepsy. Focal epileptiform activity produced in the brain of patients with complex partial epilepsy, is the result of the firing of groups of cells, the magnetic fields of which can be recorded with a sensitive instrument known as a Superconducting Quantum Interference Device or SQUID. Traditionally, scalp-recorded electrical potentials have provided estimates of the location of focal abnormal activity in the brain. Because, unlike the scalp potentials, MEG is not distorted by intervening tissues and the skull, the magnetic fields may be used to more accurately localize the epileptic focus.

Recent studies have suggested that maps of magnetic field recordings from individuals with partial epilepsy may provide accurate localization estimates for sources of abnormal activity. The present study was designed to replicate those studies and to test a technique for localizing the sources which uses the field maps as an initial estimate.

Neuromagnetic activity was recorded from two patients with medically diagnosed complex partial epilepsy. Scalp potentials (Electroencephalogram or EEG) and magnetic activity (Magnetoencephalogram or MEG) were recorded simultaneously. Abnormal electrical spike potentials, detected with a semi-automated computer algorithm, were employed to average the MEG data. Magnetic field maps were produced from the averages of sequential MEG recordings over different sites of the head. In one case, the maps revealed magnetic field patterns associated with the voltage spikes of the EEG which could be modelled as a current

dipole. The maps were used to give an initial estimate of the location of the focal interictal epileptiform activity for this patient. This initial estimate was employed within an iterative dipole localization computer program which produced dipole estimates accounting for a large amount of the field pattern variance over the scalp. Results from the dipole localization program were compared with tomographic structural images for each patient produced by Magnetic Resonance Imaging. In a second case the maps indicated field patterns of a complex nature which could not easily be explained in terms of the dipole model.

The findings are discussed with respect to current conceptualizations of source models in magnetoencephalography.

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INTRODUCTION

Magnetoencephalography (MEG) is a non-invasive technique which measures the magnetic fields associated with electrical activity of the brain. The technique of recording the magnetic fields of the brain is of interest to researchers for two reasons. Firstly, unlike the scalp electroencephalograph (EEG), the MEG arising from sources in the brain is not distorted by intervening tissues such as the skull and dura, and hence the field pattern is more focal and accurate than that of the EEG. The EEG measures volume current at the scalp which has been distorted and attenuated by intervening tissue (Geisler & Gerstein, 1961, from Cohen & Hosaka, 1976). Secondly the MEG for the large part detects the tangential component of the underlying activity, while the EEG mainly detects the radial component. Thus, the MEG may provide information not accessible with the EEG (Cohen & Cuffin, 1983). These differences between the two techniques suggest that in some respects the MEG is capable of providing additional and more accurate information about sources of activity.

Synchronized firing of neurons produces magnetic fields which are large enough to be measured with the MEG. Such synchronization occurs naturally, as in the case of background alpha activity, or may be produced experimentally, for example by sensory stimulation. In some cases, abnormal brain activity is highly synchronized, as in epilepsy which is the result of firing of groups of cells. Traditionally, scalp-recorded electrical potentials (EEG) have provided location estimates of epileptogenic abnormalities in the brain. However, because, unlike scalp potentials, MEG is not distorted by intervening tissues and the skull, the magnetic fields may be used to more accurately localize an epileptic focus.

Several authors have reported MEG findings in focal epilepsy (epilepsy which arises from circumscribed areas of the brain) (e.g., Barth, Sutherling, Engel & Beatty, 1982, 1984a; Ricci, 1983; Sato et al., 1985) mostly with the intention of investigating MEG as a tool for localizing the abnormal activity in the brain. The actual number of subjects for whom precise and verified localization has been reported is, however, small. In addition, some of the reports in the literature state that several patients are being investigated, yet discuss detailed results from a subset of those subjects (Barth et al., 1984a; Ricci, 1983). As a consequence, it is unclear whether the technique is appropriate for use in all cases of focal epilepsy, or whether the MEG is more suitable for some than for others. It also remains unclear as to whether current methods of data collection and analysis are appropriate for all patients, or whether the techniques employed will depend upon the type of case under investigation. In addition, until a larger number of cases is documented it is impossible to know the full range of variability between findings from different patients.

The intention of this study was to record the distribution of magnetic fields associated with the interictal (between seizure) EEG discharges of subjects with complex partial epilepsy (a form of epilepsy which has its genesis in focal areas of the brain), and to use these data to localize precisely the source of the abnormal activity in the brain. The technique of Magnetic Resonance Imaging, which tomographically images brain structure with a high degree of resolution, was used to verify the MEG localization. It should be noted that in the present work one of the assumptions currently used in neuromagnetometry, that of a single-sphere skull shape, was not invoked in the estimation of source location. As a result, the estimation of the distance from the source to the detector was more accurate.

EPILEPSY

Although the disorders commonly refered to as the epilepsies have no simple definition, it is clear that epilepsy is a symptom of underlying brain disturbance with an associated "paroxysmal cerebral dysrhythmia" (Gibbs, Gibbs & Lennox, 1937) rather than a specific disease process. Such brain disturbances may issue from many different pathological processes occuring in diffuse or highly localized areas of brain tissue. As a result of the variability in both pathogenesis and locality of the abnormality, the symptomatic expression of the disorder can be highly variable between patients. Epileptic expressions range from the dramatic tonic-clonic Grand Mal convulsion to subtle disturbances in behaviour which may go undetected by observers (Bosches & Gibbs, 1972).

Grand Mal convulsions are believed to involve widespread areas of the brain, hence the widespread effects of the ictal (seizure) events. In contrast, focal, or partial seizures, arise from circumscribed areas of the brain (Bosches et al., 1972), hence the more limited expressions of ictus, which show some correlation with the specific function of the brain areas involved (Pedley, 1984).

Of particular interest for this study are focal seizures appearing to arise from the temporal lobe structures or nearby structures. The constellation of symptoms which occurs in temporal lobe epileptic disorders has been well described for many years. For example, Hughlings Jackson (1870 & 1888, from Gastaut, 1954) was well aware of the behavioural and experiential symptoms of partial seizures and attributed them to a lesion or 'mechanism' in the uncus or nearby structures. As previously noted, the exact location of the abnormalities in the temporal

lobe is often unclear, although scalp Electroencephalography (EEG) will indicate a focus in the temporal area. Thus, the disorder is referred to in the literature by several different names: Temporal Lobe Epilepsy (TLE), the term preferred by Penfield and Erickson, 1941 (cited in Bosches et al., 1972); Psychomotor Epilepsy (Gibbs et al., 1937), and Partial Complex Epilepsy (PCE) (Gastaut, 1970). The particular term preferred by various authors reflects either preference to describe symptoms, as in the case of psychomotor and partial complex epilepsy, or presumed area of seizure origin, as in the case of temporal lobe epilepsy. The term temporal lobe epilepsy has been criticized on the grounds that there is substantial evidence to indicate that so-called temporal lobe seizures can be experimentally induced by stimulation of deep structures such as the hippocampus or the uncus, as well as from a superficial focus (Jasper, 1941; Gastaut, 1954). The disorder will be referred to throughout this discussion as partial complex epilepsy (PCE).

PCE is ictally expressed as automatic behavioural activity such as picking at clothes, gustatory phenomena and lip smacking, psychic manifestations, and disturbances in consciousness (Gastaut, 1970). All or some of these symptoms may be present in any one seizure, although within patient variability is not substantial. There have also been many reports characterizing interictal behavioural changes which include such symptoms as hyposexuality, perseveration, hypergraphia and rigid morality (reviewed in Lishman, 1978). Without doubt seizures can be very disruptive and the effective control of seizures is essential for the medical and social well-being of the patient (Rasmussen, 1975). In most cases medication is effective in this regard; however, some 30% of patients remain refractory to traditional medical intervention (Wilder, 1971). Focal epilepsy, including that with elementary and complex syptomatology, is the most common form of epilepsy in the adult population (Gastaut, Gastaut,

Gonclaves de Silva & Fernandez Sanchez, 1975); partial complex epilepsy is in turn the most common of the focal epilepsies (Pedley, 1984).

THE ELECTROENCEPHALOGRAM IN EPILEPSY

The analysis of scalp-recorded electroencephalographic (EEG) activity has provided the traditional technique for localization of the irritative brain foci of epileptic patients. The major EEG finding in epilepsy has been spike or sharp wave activity, first described in 1929 by Berger. His observations have been repeatedly confirmed since that time, both with routine resting EEG recordings and with special activation techniques such as intravenous metrazol (Gloor, 1975). Spike and sharp wave discharges are discrete events which are generally of higher voltage than the background activity (Pedley, 1984). The 'sharpness' or duration of the wave determines its classification as a spike or sharp wave. Spikes are defined as having a sharp outline and a duration of approximately 80ms or less, while sharp waves have a duration of 80-200ms (Storm van Leeuwen et al., 1966). The duration appears to reflect the synchrony of the discharging group of cells (Gastaut, 1954; Pedley, 1984). Spikes and or sharp waves may occur in the inter-ictal EEG as well as in ictal recordings (Golla, Graham, Walter & Camb, 1937); this feature allows for the identification of epileptogenic events without seizure activation. The specific patterns of EEG changes associated with different types of epilepsy were documented in 1937 by Gibbs et al., and although their findings, and therefore their descriptions, were modified by their recording technique (Walter, from Gastaut, 1953), they were the first to differentiate EEG findings in partial complex epilepsy. Although interictal spikes or sharp waves are extremely useful in the diagnosis of all forms of epilepsy, several authors have pointed out that the spike

focus of the interictal EEG, especially in PCE, is not necessarily identical with the epileptogenic area. Thus, for maximum localization, even with depth recordings, it is necessary to record during seizure onset (Gloor, 1975; Ludwig, Ajmone Marsan & Van Buren, 1975; Talairch & Bancaud, 1966).

Although the major advantage of the scalp-recorded EEG is its non-invasive nature, its localization power is somewhat limited. There are four major reasons for this: Firstly, intervening tissues and substances (i.e., the meninges, cerebro-spinal fluid, skull, scalp and brain tissue) possess different resistivities, resulting in distortion of the electrical potentials recorded at the scalp (Cuffin & Cohen, 1979). Secondly, these factors contribute to attenuation of the scalp-recorded neuronal activity. Estimations of attenuation based on simultaneous recordings from scalp and from brain tissue have varied: 10-to-1 (Penfield & Jasper, 1954), 60-to-1 (Abraham & Ajmone Marsan, 1958), or as much as 150-to-1 (Goldensohn, 1979; Pedley, Traub & Goldensohn, cited in Pedley, 1984). The degree of attenuation has been demonstrated to be due to two major factors: (1) the size of the cortical area involved (Pedley, 1984), and (2) the frequency of the signal, higher frequencies (especially above 15Hz) being attenuated to a greater degree than lower frequency signals (Pfurtscheller & Cooper, 1975). Thirdly, it has been reported that some cortical potentials are not detectable at the level of the scalp (Abraham & Ajmone Marsan, 1958). Fourthly, scalp recordings represent the averaging of neuronal aggregates (Pfurtsceller & Cooper, 1975), and volume conduction (Cohen & Hosaka, 1976). Thus, in cases of operable refractory epilepsy, the routine EEG is now supplemented with recordings from subcortically or cortically placed electrodes.

SURGICAL INTERVENTION IN EPILEPSY

As previously mentioned, drug therapy is the most common approach to seizure control in epilepsy, with an estimated 70% success rate (Wilder, 1971). The remaining 30% of refractory cases must rely on other methods of control. Surgery is most effective in cases with clear-cut lateralization of the focus. However, with bitemporal abnormality, the success rate is very much reduced, especially when the lobe selected is incorrect (Wilder, 1971). Clearly, accurate foci localization determines the success of surgical therapy. Accurate localization is presently achieved with the placement of cortical and subcortical electrodes as mentioned above (Cooper, Winter, Crow & Walter, 1965). Surgically placed electrodes offer the significant advantage of relative proximity to the source of abnormal electrical activity, thus circumventing the problems of scalp EEG. Unfortunately, these techniques also have serious disadvantages including the risk of further tissue damage and the possibility of sampling error. Because invasive electrodes are only placed in areas which are resectable (Crandell, 1983, cited in Sutherling, 1985), it is neither feasible nor ethical to sample all brain structures. It is also impossible to replace the electrodes once they have been positioned (Taliarch & Bancaud, 1966). These disadvantages have been, in part, responsible for the current interest in developing new, non-invasive techniques for localization. The magnetoencephalogram presently provides one of the most promising approaches to non-invasive localization of epileptic foci.

OVERVIEW OF MEG STUDIES IN EPILEPSY

Cohen (1972) provided the first report of epileptic activity recorded

by the MEG. He described delta activity (at 1-2 Hz) in the MEG of a patient with PCE during hyperventilation. Hughes (1977) subsequently studied several patients with different neurological abnormalities including some with petit mal absence, and its concomittant 3 per second spike and wave EEG pattern. His report was particularly interesting in that although EEG spikes and harmonics of them were well represented in the magnetic fields, the slow wave was frequently undetected by the MEG. Although Hughes speculated that different generators were responsible for the two major components (spikes and waves) of this classic EEG discharge, he made no attempt to localize the intracranial generators of the spikes.

Single channel systems preclude the simultaneous study of widespread activity. As a result, focal epilepsies are more accessible to study with the MEG than are the generalized epilepsies. Findings in 36 patients with various brain dysfunctions, including focal epilepsy (Modena, Ricci, Barbanera, Leoni, Romani & Carelli, 1982), indicated the usefulness of MEG in the partial epilepsies. This was the first published attempt to investigate the relationship between interictal spiking in the EEG of focal epileptics and changes in the MEG. Computerized tomography (CT) for verification of localization was believed to support the MEG localization of source. The conclusions indicated that the largest correspondance between MEG and EEG spikes occured in the condition of a superficial epileptic focus on the lateral surface of the cortex as confirmed by CT scan. These authors did not use the techniques of spike averaging or mapping reported in a study by Barth, Sutherling and Beatty (1982).

Averaging of the interictal spikes provides improvement in signal-to-noise ratio and reliability (Picton & Hink, 1973), both of which improve with the number of spikes in the average. Averging is accomplished by using the EEG spike as a trigger for entering that portion

of EEG and MEG data into the average as a trial.

Mapping techniques for visualization of the fields have proven to be an excellent method to reduce data and study the spatial and temporal dynamics of the MEG. Perhaps more significantly, maps can be helpful in three-dimensional localization of the putative dipole generators.

The Barth et al., (1982) study which utilized averaging and mapping reported results from two patients, one with right focal temporal interictal spiking and an homologous contralateral focus in the left anterior temporal region, and the second with a unilateral anterior temporal interictal spike discharge. For the positioning of the SQUID (Superconducting QUantum Interference Device) these authors designed a rectangular grid of recording positions (28 points 2cm apart) centred around the electrical focus. In the case of the first patient it was demonstrated that there were two dipole generators, one in each hemisphere, the left being dependent upon the right and occurring at a somewhat delayed latency believed to be due to transcallosal discharge from the right hemisphere. Two maxima in each hemisphere were demonstrated which permitted the fit of simple dipoles, one in each hemisphere. In the second patient with unilateral spiking, a single dipole source was detected, although apparently there was no recording of MEG over the hemisphere contralateral to the spike. With the assumption that the interictal spikes could be modelled as a current dipole, the isocontour maps were used to make estimations of depth, location and orientation of the source.

Cohen's original report in 1972 suggested that the MEG might contain information not present in the EEG. This was confirmed in 1983 by Ricci who reported the finding of MEG spike activity which was not

simultaneously recorded as electrical spikes with surface EEG electrodes. This report also found that EEG sharp waves would at times be resolved into poly spikes in the MEG, thus leading the authors to conclude that MEG has a higher temporal resolution than EEG. This finding has yet to be duplicated by other researchers. In a later experiment (Ricci, Buonomo, Romani, Salustri & Modena, 1985b) by the same principal author, similar findings were reported. A total of 60 patients were investigated in the 1983 study, 58 of whom had been studied in sufficient detail to warrant report. All 58 suffered from epilepsy, some generalized, and some secondary to tumor. Thirty-two were known to have PCE and, in 14 of those cases, computerized tomograms (CT) showed abnormalities. Methodological limitations prevented these authors from pin-pointing the two areas of maximal MEG activity of opposite polarity (fields coming out of the head and fields going into the head) which would satisfy a simple current dipole model. By counting the number of spikes at each recording position, the authors designated areas of maximal activity which were observed to fade gradually, or sometimes abruptly, as the detector was moved away from the area. There are several possible reasons for their findings: Firstly, counting the number of spikes at a given recording location provides no information about amplitude or polarity. Secondly, the recording locations appear to have been limited to areas of the scalp, above the subject's ears and eyebrows. Pilot data for this study and other reports (Barth et al, 1982) clearly demonstrates the necessity of recording over the cheek area of the face, and below the occiput in some subjects. Thus, while polarity reversals were not reported, two maxima may have been observed had the recording sites been over an extended area (if one assumes that the number of spikes varies with distance from the source). Whether this would be the case is unclear, as it would seem more reasonable to expect differences in amplitude and polarity of the spikes, rather than in the number of spikes, as the gradiometer is moved to

different positions over the head. Failure to detect a second maximum rendered it impossible for these researchers to approximate source depth from the MEG. In the 14 cases with abnormal CT scans, the areas of maximal activity and structural abnormality were similar (Ricci, 1983).

Two reports published in 1984 (Barth, Sutherling & Beatty, 1984; Barth, 1984) added significant information to the MEG-epilepsy literature. The first report (Barth et al., 1984) investigated multiple source generators of epileptiform activity. Eight out of 17 patients with focal epilepsy showed spatio-temporal discharge patterns in the MEG which appeared to be generated by more than a single source (particularly evident in two cases). In these patients it was possible to identify two sources of MEG activity within the same hemisphere which differed in location and orientation. Identification of the two different sources could be made not only on the basis of MEG spike onset differences but also on the basis of differing spike morphology. For both cases it was possible to fit the data to two dipoles which differed in orientation and location and showed a discharge sequence, one following the other. In a conference report of the same data (Sutherling, Barth & Beatty, 1985) the importance of distinguishing interictal propagation patterns (preferred patterns of discharge) as a means to identify the primary focus was discussed. It has already been demonstrated in electrophysiological studies that interictal propagation patterns exist (Buser et al., 1983, from Sutherling et al., 1985), and it was argued that the most important component in the pattern for treatment and localization purposes is the primary discharge source (Sutherling et al., 1985).

In his second report Barth (1984b) studied an animal model of epilepsy. Previously, the recording of MEG was believed to be untenable in small animals, such as rats, because of the relatively large coil

diameter and relatively small brain. Barth argued that the problem could be circumvented if proper attention were given to the diameter and separation of the gradiometer coils. Metrazol seizure induction in humans is unethical when the investigators are limited to single channel MEG data collection. The use of animals permits the investigation of ictal events. In Barth's experiment, seizures were produced in four rats by injection of penicillin into the cerebral cortex, 2mm lateral to the midline on the left side, which produced stereotyped focal epileptic spiking in the electrocorticogram (ECoG) and seizures. The most apparent response in the MEG to these induced focal seizures in all 4 animals was a steady magnetic field shift from pre-seizure baseline. This shift dropped abruptly back to baseline at the end of the seizure. The time course and the amplitude of the MEG shift varied between animals, but was stable within animals. The magnetic fields observed were consistent across animals, indicating magnetic flux emerging from the right side of the brain and reentering on the left. Spiking during seizure was also recorded by the MEG, which was of lower amplitude than the slow activity. The slow shifts recorded with the MEG in this study were similar to d.c. electrical shifts reported by by other authors using penicillin-induced seizure activity (Caspers & Speckman, cited in Barth, 1984). Although d.c. shifts are believed to be a physiological characteristic of seizures, they have not been studied extensively in the EEG because of technical difficulties arising from polarization voltages at the electrode-scalp junction (Cohen, 1972). Barth proposed three advantages arising from animal model MEG investigations: 1. there is no contact between the recording device and the brain, thus no problem with polarization. 2. SQUID magnetometers have a wide frequency response (0 to 10KHz). 3. in this kind of experiment the activity produced is stereotyped, not showing the variability seen in most human studies.

Several conference presentations have included data collected for the investigation of the MEG in epilepsy. While a few have added to the understanding of epileptic phenomena as recorded by the MEG, others have suggested different techniques for use in data collection. What follows is a brief summary of the material presented by those authors.

One research group discussed findings in studies of comparisons of MEG, EEG and electrocorticography (ECoG) (Sato, Sheridan, Smith, Bonner & Weinstock, 1985). This type of research is fundamental to the claims that the MEG may provide information equivalent to that provided by depth electrical recordings. Unfortunately, MEG activity was not mapped and there was no attempt to localize other than by comparison to the EEG. However, the ability of the MEG to detect EEG spikes which could be recorded from the cortex but not the scalp was investigated. In one of the subjects, it was found that neither the MEG nor the EEG detected spikes from a cortically (ECoG) recordable focus. The cortical recording demonstrated bilateral spiking primarily located at the right frontal tip of the temporal lobe. Although neither the MEG nor EEG was recorded simultaneously, independent records had shown that both techniques demonstrated high voltage saw-toothed delta activity. This activity occurred at about the same frequency as the cortical spikes, but the spiking seen on the ECoG was not recorded. The delta activity shifted in and out of phase with the EEG and, when out of phase, the MEG lagged behind the EEG. The MEG and EEG recordings suggested a non-cortical discharge. However, the ECoG definitely suggested cortical discharge on the basis of amplitude and frequency. Sato et al. pointed out that this finding did not support Ricci's (1983) conclusions that the MEG detects superficial spikes, and that slow waves in the EEG correspond to spikes in the MEG. It was speculated that the MEG might not have observed the spikes due to radial orientation of the dipole. However, as the authors

pointed out, this does not explain why the EEG did not detect the spikes. It is unclear exactly how many recording sites were used for the MEG. Possibly the spike was not visible because of the areas sampled over the head. In the second patient, EEG, ECoG and MEG spikes showed similar morphology. The findings led the author to speculate that abnormal source current may be affected by other surrounding currents which may distort the MEG (Sato et al, 1985).

A second conference report (Sato, Rose & Porter, 1985) examined the merits of mapping single spikes of similar morphology, as opposed to mapping from an average of spikes. The authors argued that in many cases spike morphology, reflected in amplitude, duration and maximal distribution, may vary within patients and within a focus, and that this variability may contain information that is lost in the averaging procedure. In an exploratory study, the investigators selected representative spikes from each MEG position and were able to map two extrema of opposite polarity which fit the simple dipole model. In the future the authors plan to compare this technique with that of the averaging procedure. Further comparison with multichannel systems may permit the discrimination of shifts or spread in the dipole over time. Others have already carried out single spike mapping (Sutherling et al., 1985). They found that, whereas in some cases mapping of selected single spikes can result in orderly field maps, it fails to do so in other cases. These latter cases, however, do show orderliness once the usual averaging procedure is used (Sutherling et al., 1985).

Most, if not all, authors rely on the simplifying assumption of an equivalent dipole source. This type of source is represented in a typical manner by isocontour maps. Sutherling, Barth and Beatty (1985) described examples of isofield line distortion from that expected in the case of an

underlying equivalent dipole. Two types of distortion were apparent: 1. in the single source case, there were instances in which the lower part of the map (vertex at the top) looked less dipolar than the upper part of the map and, 2. distortions in the maps of multiple sources appeared in more central parts of the map.

In the case of the first type of distortion, it was speculated that the recording may have been contaminated with artefact arising form non-radial measurement over the ear, mastoid process and jaw, below the brain and distant from it. Alternatively, the activity may have been non-artefactual and therefore indicate more complex sources for which the equivalent dipole model is inappropriate. In the later case, it was reported that the distortions appeared in areas which show subsequent maxima, or in other cases previous maxima mimicking the persistence of fields. It was further hypothesized that the data were due to a single extended, simultaneously active, dipolar sheet in which the orientation of the electrical currents was changing, thus giving the impression of multiple sources. The authors concluded that the different interpretations could eventually be tested by intracranial electrical techniques.

When the data are not suitable for averaging, for example, when the interictal spikes are not of high enough voltage to be used as triggers, a procedure known as relative covariance (R.C.) can be used (Chapman, Ilmoniemi, Barbanerra & Romani, 1984). In this procedure one EEG channel is used as a reference for each recorded MEG position. The covariance between the MEG for each position and the reference EEG channel is calculated, which is then divided by the variance of the reference EEG. The division by the electrical variance compensates for variations in the strength of the source (Chapman et al., 1984). Ricci et al. (1985b),

confirmed the usefulness of the relative covariance technique in the investigation of epilepsy. They demonstrated substantial agreement between R.C. and averaging techniques when used for localization purposes.

The limitation of a single channel for MEG recording has long been recognized. Single channel systems necessitate sequential recordings from different sites, thereby demanding the assumption that the underlying source remains constant. The most recent report in the literature on neuromagnetometry in epilepsy comes from the Rome group (Ricci, Buonomo, Romani, Sulustri & Modena, 1985), in which they briefly reported their first results using a four channel recording system. Localization did not always agree with that derived from the EEG, and the MEG suggested poly focal activity unsuspected on the basis of the EEG alone, a finding which has been reported previously (Ricci, 1983).

SUMMARY OF MEG AND EPILEPSY REPORTS

The literature described has included several studies which appear to indicate that MEG shows significant promise for accurate localization of dipole sources in epilepsy. However, the actual number of reported and confirmed localizations has been limited. The total number is fourteen, eight of which were contained in an extremely brief report (Ricci, 1985b) for which the localization was quite general, for example "right mid-temporal area". This leaves a total of six patients for whom estimation has been precise and verified by medical imaging techniques.

Overall, the technique requires the collection, analysis and report of data from many more patients. MEG is a lengthy procedure, and CPE is not an homogeneous disorder, thus, it could be a number of years until the

exact contribution of the technique to epileptology is known. Further, it is important to continue to compare dipole location estimates with converging evidence from other techniques, such as MRI, CT and ECoG, at least until MEG has been proven accurate enough for use in patients with normal MRI's and CT's.

Several other interesting findings have been reported in the literature described including propagation patterns and the distortion of iso-field lines discussed by Sutherling et al. (1985), d.c. shifts during seizures reported by Barth et al. (1984b), the temporal resolution differences between MEG and scalp-EEG described by Ricci (1983) and the single spike mapping (Sato et al., 1985a). All point to the need for an extension of the analyses and data collection currently in use.

The present study was undertaken to use the MEG to accurately localize the sources of interictal discharges in epileptic patients. The structural abnormalities detected by the MRI were used to verify the results. MRI was chosen because of its high resolution. It must be noted that in this study, as in other sudies, the localization is of the interictal activity which may not arise from the same area as ictal discharges, however, one of the issues in this study was the usefulness of localizing interictal activity.

METHOD

Subjects

Two subjects with complex partial epilepsy completed the study. The first was a 21 year old female (DOH) with partial complex epilepsy. The onset of seizures was at 7 years of age following mumps encephalitis. Seizures were poorly controlled with medication which was tegretol and valproic acid. Previous scalp-EEG showed an interictal spike focus in the region of the right mid-temporal area, and a second focus in the left mid-temporal area which appeared to be dependent upon the right-sided focus.

The second subject (RZ) was a 28 year old male with seizure onset at age 16 years. At the time of the study the reported seizures were of two types: Generalized tonic-clonic seizures which were controlled with medication, and partial complex seizures which had been under poor control for the previous ten months. Medications were valproic acid and dilantin. Previous scalp-recorded EEG had shown a "focal irritative disturbance" (spike discharge) in the right anterior temporal region.

Data Collection

Computer models of the head were produced by digitizing points over the scalp and face with a mechanical digitizing arm which can be mounted on the side of the dewar. An origin within the head was estimated by the program for each subject from points digitized at the nasion, inion and pre-auricular points. A computerized gantry system (Vrba et al., 1982) used the models to direct the gradiometer to pre-selected recording positions and stored information regarding the final recording angles of

the system for use in later analyses of the data.

Interictal EEG and MEG were recorded simultaneously and monitored on a Mingograph polygraph. Gold EEG electrodes, placed in accordance with the International 10-20 placement system (Jasper, 1958), and additional surface sphenoidal leads (Sph), formed the following montages for the subjects: For subject DOH, Fp2-Right Sph, F8-T4, T4-T6, T6-O1, Fp1-F7, F7-T3, T3-T5. For subject RZ, F4-F8, F8-Right Sph, Right Sph-Left Sph, Fp2-F8, F8-T4. The surface sphenoidal electrodes were placed below the sphenoid bone, over the zygomatic arch. Each patient lay on a mattress on a wooden bed, in positions suitable for recording over various parts of the head. The state of the subjects varied from relaxed alertness to light sleep. The digitizing arm was used to locate three landmarks on the patient's head: nasion, inion and right or left preauricular point, which located the position of the patient's head in space for use by the computerized gantry. The gradiometer was sequentially moved by the gantry to a number of different locations (75 for DOH, 44 for RZ), 1.2 centimeters away from the head. Manual corrections were made for distance of the dewar to the head and for keeping the dewar normal to the skull. The MEG recording positions used in the data analyses are shown in Figure 1 for DOH and 2 for RZ. Figure 3 shows the 10-20 positions with an inset radius equal to that of the MEG recording position diagrams to show the relative head positions at which the recordings were made. A superconducting quantum interference device with a 3rd order asymmetrical configuration (Vrba et al., 1982) was used to record the MEG. One channel of MEG and three channels of EEG were continuously collected in 8 second intervals (256 points per second), digitized, and stored on line with a PDP 11/34 for subsequent analysis. Log files were made which contained information about the recording position of the dewar with respect to the head model. Filters settings of .5-30Hz were used for the EEG. For the

MEG digital filters were set at .5-64Hz; a 60Hz notch filter was also used.

Processing

In off-line analysis, epileptiform spikes (at F4-F8 for RZ, and Fp2-RSph for DOH, for all MEG positions, and in addition in the case of DOH T3-T5 for left hemisphere MEG positions) were detected in the subject's EEG with a semi-automated peak detection computer algorithm (based on the computation of the maximum second finite derivative of each spike). These spikes were used to identify one-second epochs of co-occuring MEG, 512ms preceding and following the spike. MEG epochs, so identified, were averaged for each of the gradiometer positions. Only averages which included three or more spikes were included in further analyses, which resulted in 35 positions for subject RZ, and no change in the number for DOH. Because of large amounts of low frequency noise, baseline corrections were made on RZ data by subtracting the mean of the first 100 data points for each position. Isocontour-line field maps, based upon the averaged MEG waveforms for each subject, were produced (Weinberg et al., 1985) to provide inital estimates of dipole location. Dipole depth, orientation and strength was estimated at specific points in the data (512 and 572ms for DOH, and 536ms for RZ) with a simplex procedure (Harrop et al., 1986), and the solution compared with structural abnormalities detected by Magnetic Resonance Imaging (MRI) for each subject. For subject RZ a simultaneous 2-dipole fit was computed. Two single dipole fits were also obtained for selected data from time point 536ms (see Figure 4).

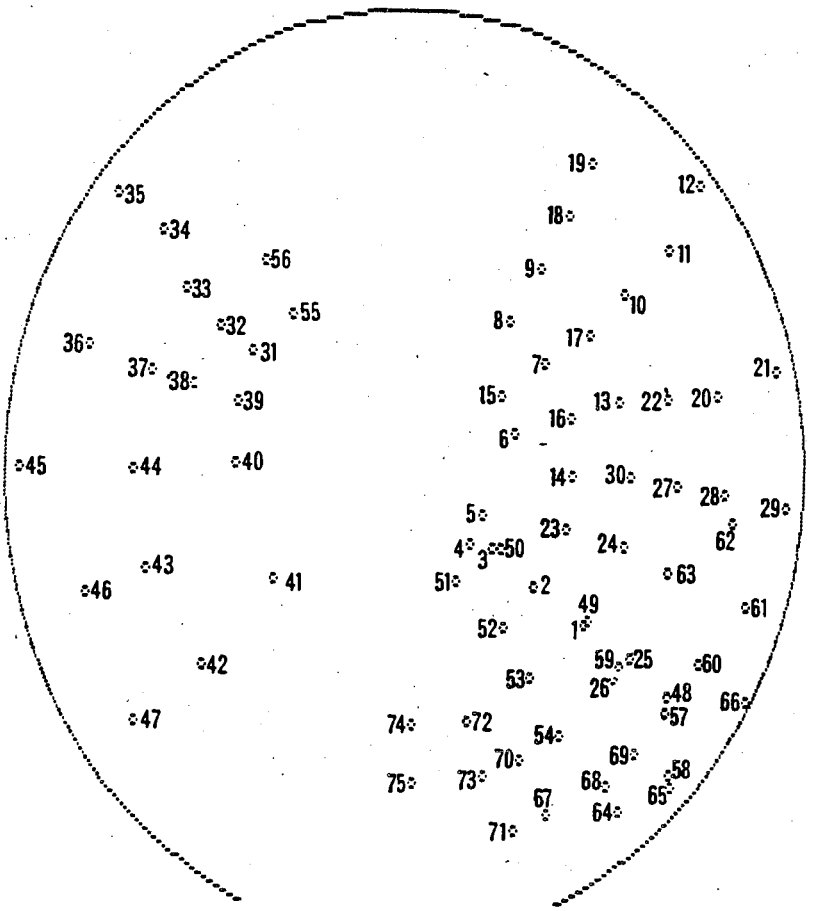


Fig. 1 MEG recording positions for subject DOH in chronological order of collection.

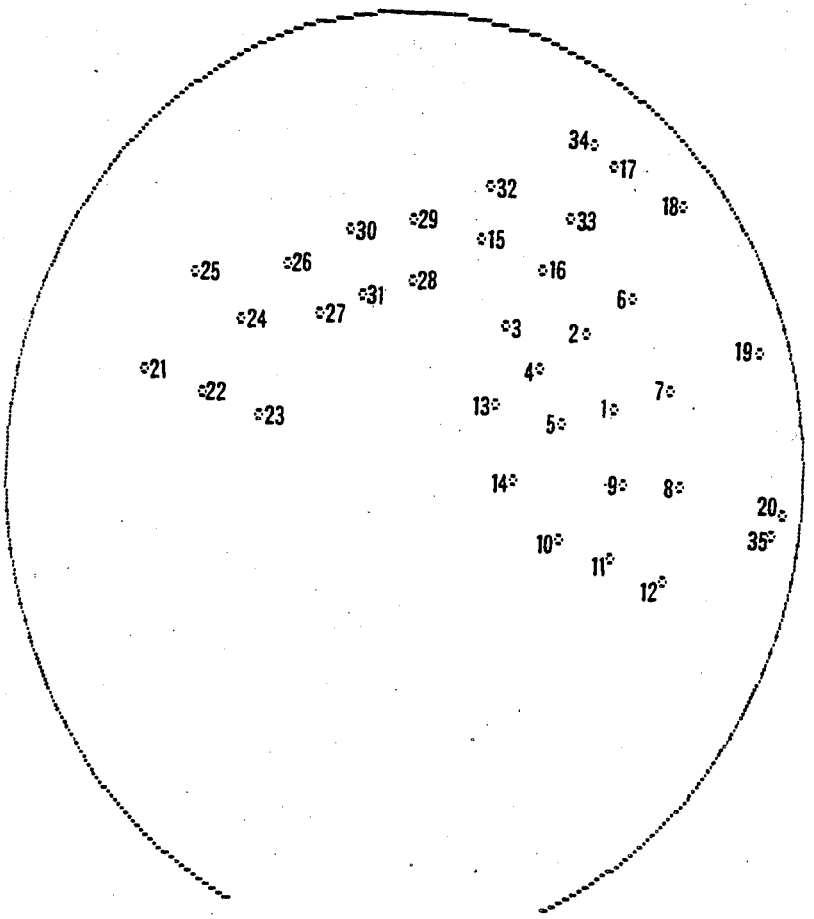


Fig. 2 MEG recording positions used in the analysis for subject RZ in chronological order of collection.

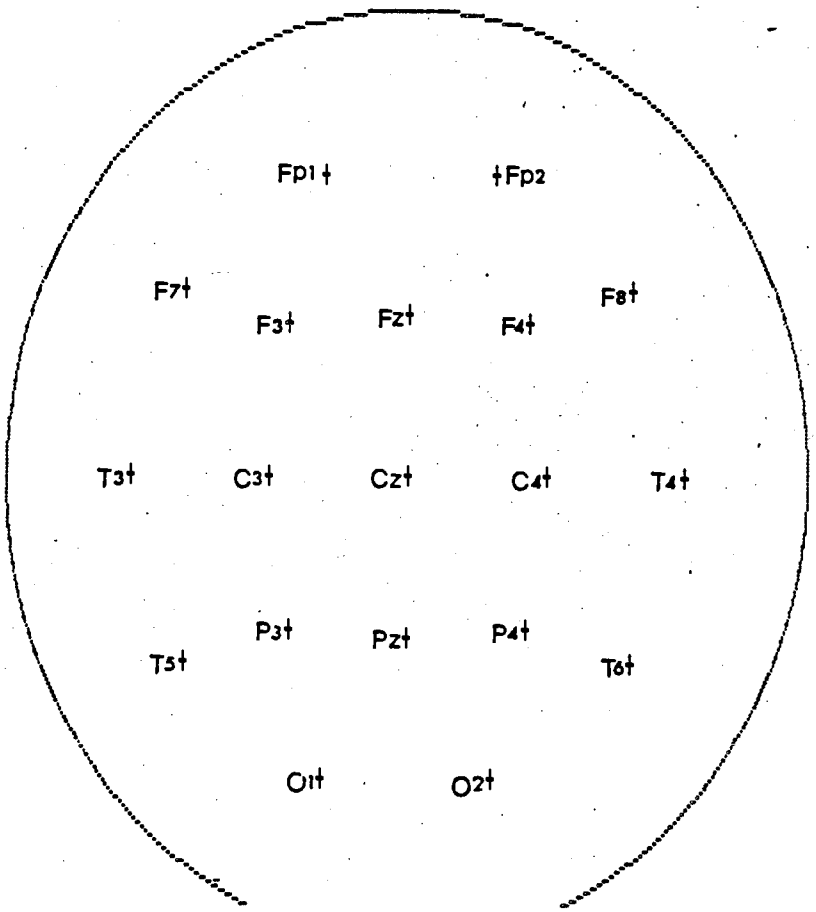


Fig. 3 The 10-20 system of electrode placement with inset radius equal to that of the MEG recording position diagrams.

Figure 4 Selected data points for single dipole fits for subject RZ.

A: Data points within box are those used for anterior dipole fit, plus the blacked-in point over the left hemisphere.

B: Data points within box are those used for posterior diplole fit plus the blacked-in point over the left hemisphere.

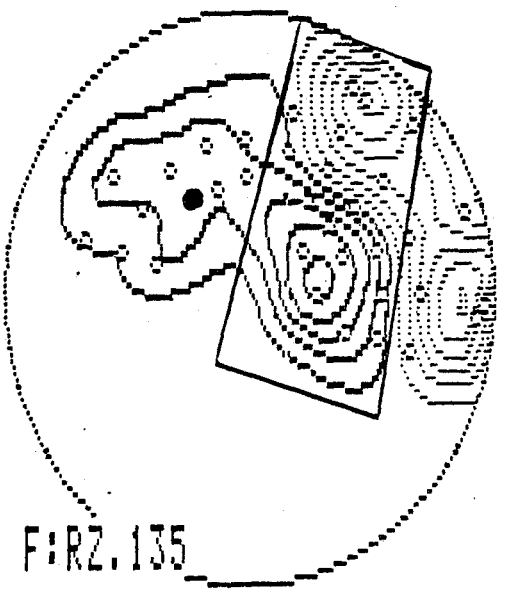


Fig 4 A.

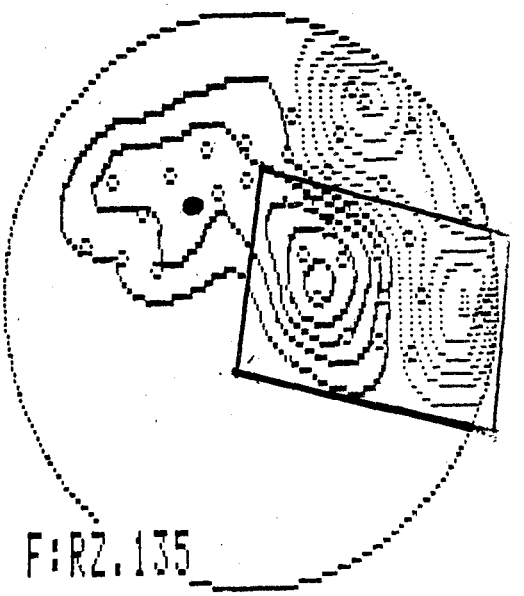


Fig. 4 B.

RESULTS

The scalp-EEG of subject DOH showed both a right mid-anterior temporal EEG spike discharge as well as a left hemisphere discharge in the homologous region. Most frequently the spikes occurred bilaterally, although at times the right sided discharge occurred independently of the left hemisphere spikes. Subject RZ showed right anterior temporal EEG spiking. These EEG findings were consistent with reports of previously obtained hospital EEGs.

Averaged magnetic spikes for each MEG recording position are shown in Figures 5A (subject DOH) and 7A (subject RZ), while keys for the plots are shown in Figures 5B and 7B. A polarity reversal can be seen for each subject although this reversal is clearer for DOH than for RZ. For DOH and RZ respectively, the peak polarities occur at areas a1 and b1 representing fields emerging from the head, and a2 and b2 representing fields reentering the head. These peak polarity reversals are accordant with expected results in the case of activity which can be modelled as a current dipole tangential to the surface of the head (Williamson Kaufman, 1981). The grand average EEG plots demonstrate the relationship between the MEG and EEG. For DOH, despite the active EEG spike over the left hemisphere, averages triggered either from the right or left hemisphere EEG spikes did not result in clearly associated MEG activity. Enlargements of two waveforms from the right hemisphere, one near the maxima, the other near the minima, are shown in Figure 6, to demonstrate more clearly the relationship between them.

The plots for RZ show two areas where the fields leave the head. The

first component of the spike complex (the MEG activity associated with the negative peak of the EEG spike) is absent in all but a few of the average waveforms, which gives the appearance of a phase lag in the MEG.

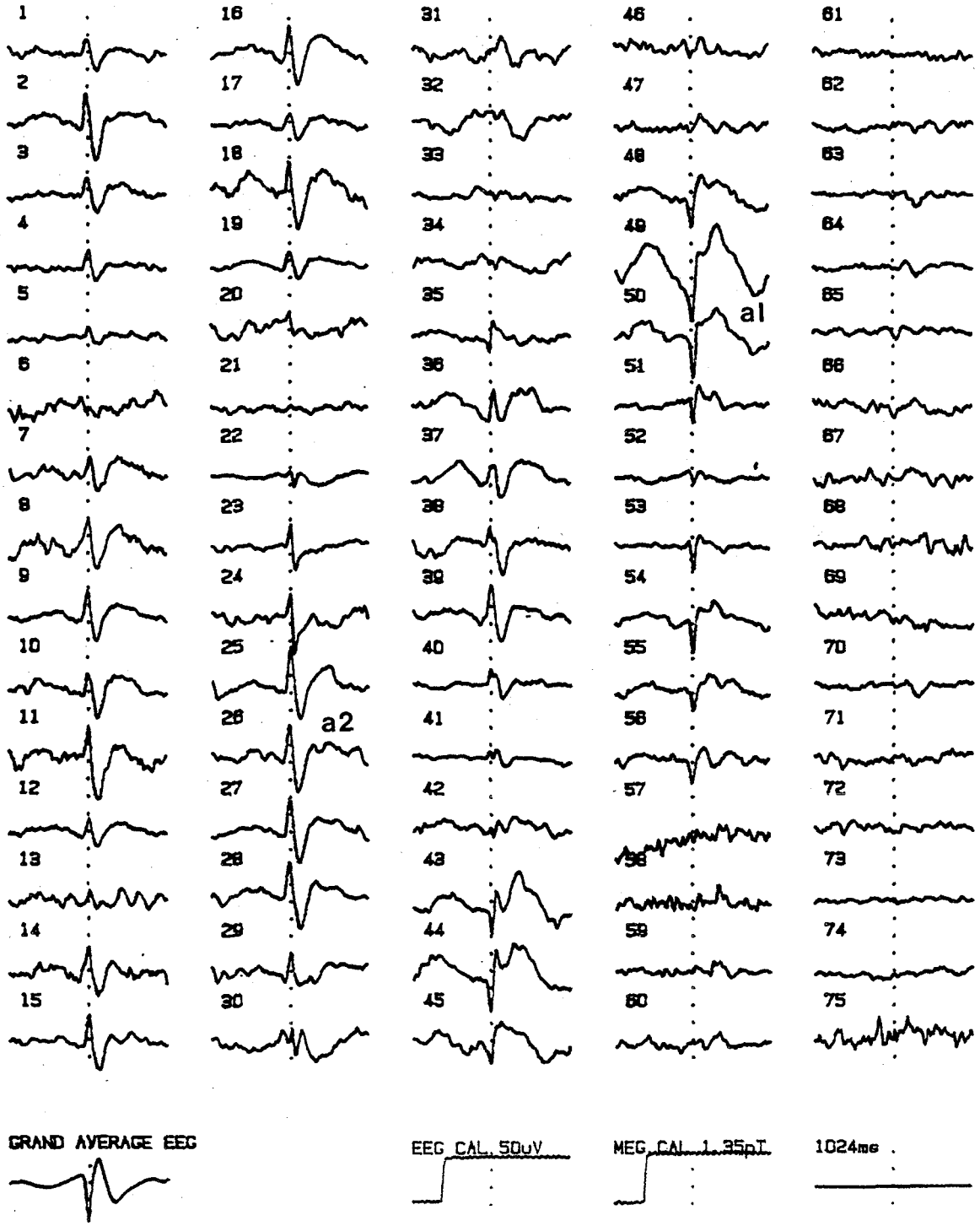
Figures 8 and 9 show contour maps, derived from the averaged data, from 400 to 796msec for DOH (Fig. 8) and for RZ (Fig. 9) respectively. For subject DOH there is a clear dipolar field configuration over the right mid-temporal region which peaks at 512ms (DOH.129), at the apex of the EEG spike. The dipolar field decays over the following 20ms and is followed by a gradual build-up of a second dipolar field of opposite polarity which peaks at 572ms (DOH.144) (a field inversion). Consistent with the plotted waveforms, it becomes apparent that there is more than one dipolar field configuration late in the epoch at 536ms (RZ.135). These appear to share a maximum. The first minimum is over the right mid-temporal region and is followed by a second over the right anterior-temporal region. This maximum dipolar distribution does not occur until 536ms and the field inversion corresponding to the positive component of the EEG spike is not recorded. At the mid-point of the epoch only fields re-entering the head are seen in the maps, which are consistent with the plots which show mid-epoch peaks in the same area of the head.

Table 1 shows the results of the dipole location estimation with respect to the digitizer-estimated origin, for subject DOH. The dipole position as estimated by the program can be approximated to arise from the right hippocampal region, at a site adjacent to the MRI abnormality (for data from DOH.129). The MRI was interpreted as showing sclerosis in the right hippocampus (D. Li., personal communication, 27th August, 1986). Figure 10 shows the MRI with the dipoles indicated by arrows.

The same procedure, except with a two dipole fit, was applied to the data from RZ . Table 2A shows the results of the simultaneous two dipole fit for the RZ data at 536ms. This procedure was attempted twice with different starting points for the dipoles. In the first solution the dipoles were both fit to the left hemisphere. In the second solution one of the dipoles was fit outside the head. Because the results were inconsistent with known anatomy, selected parts of the data were used in the localization program, specifically, data points which included either the more anterior dipolar field, or more posterior dipolar field (see Figure 4). Table 2B shows single dipole solutions for data selected either for the anterior dipolar distribution, or the posterior dipolar distribution. Figure 11 shows the MRI spin-echo with the dipoles (estimated from the selected data) indicated by arrows. It can be seen that the program produced a fit adjacent to the MRI abnormality for the 'anterior' data. The MRI demonstrated a vascular abnormality in the right uncus of this patient (D. Li., personal communication 27th August, 1986).

Fig. 5 A: Plots of averaged magnetic data from each recording position for subject DOH. Grand average EEG (F4-F8), negative down.

B: Key for plots; note that for presentation purposes the position numbers are not in chronological order.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GRAND AVERAGE EEG
EEG CAL. 50uV
MEG CAL. 1.35pT
1024ms

Fig. 5A

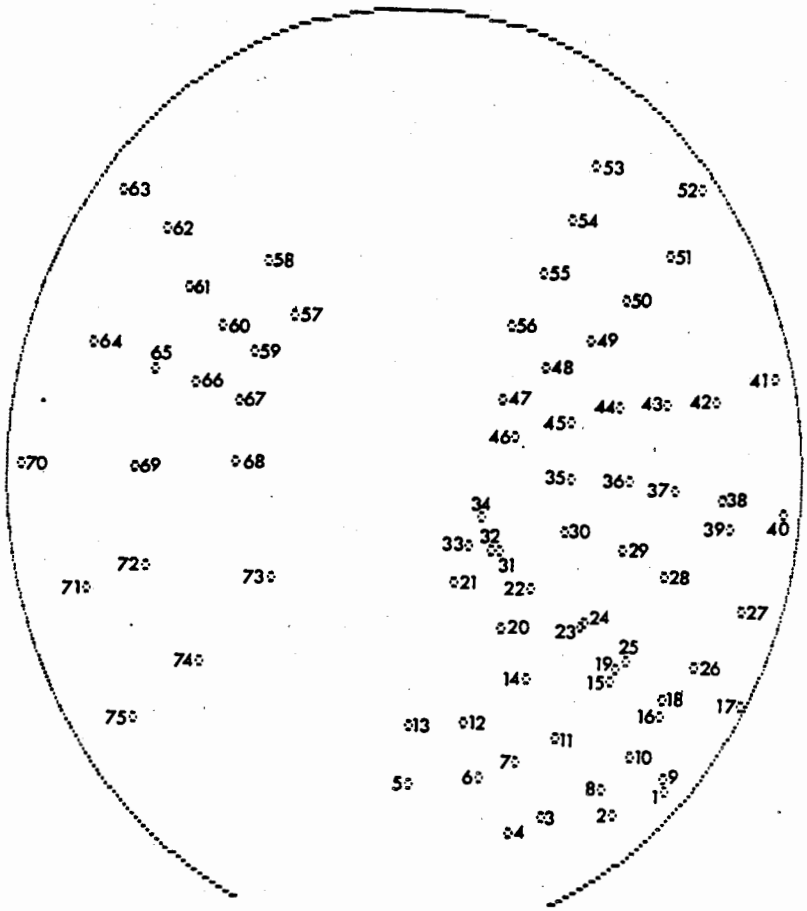
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Fig. 5 B.

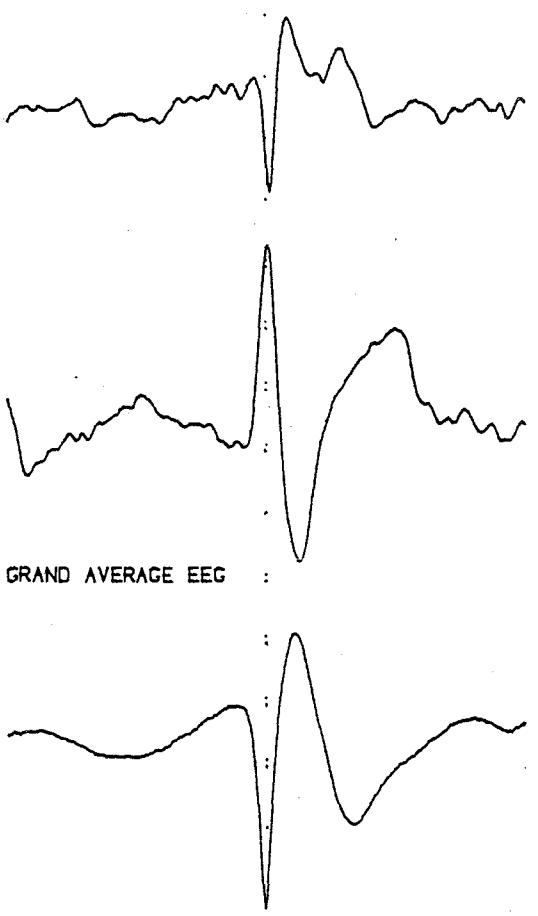

Fig. 6 Enlargements of selected average magnetic plots for DOH from two positions, one near the maxima, the other near the minima. The grand average EEG is included for comparison.

Fig. 7 A: Plots of averaged magnetic data for subject RZ.
Grand average EEG (Fp2-RSph) negative down.

B: Key for plots; note that for presentation purposes the position numbers are not in chronological order.

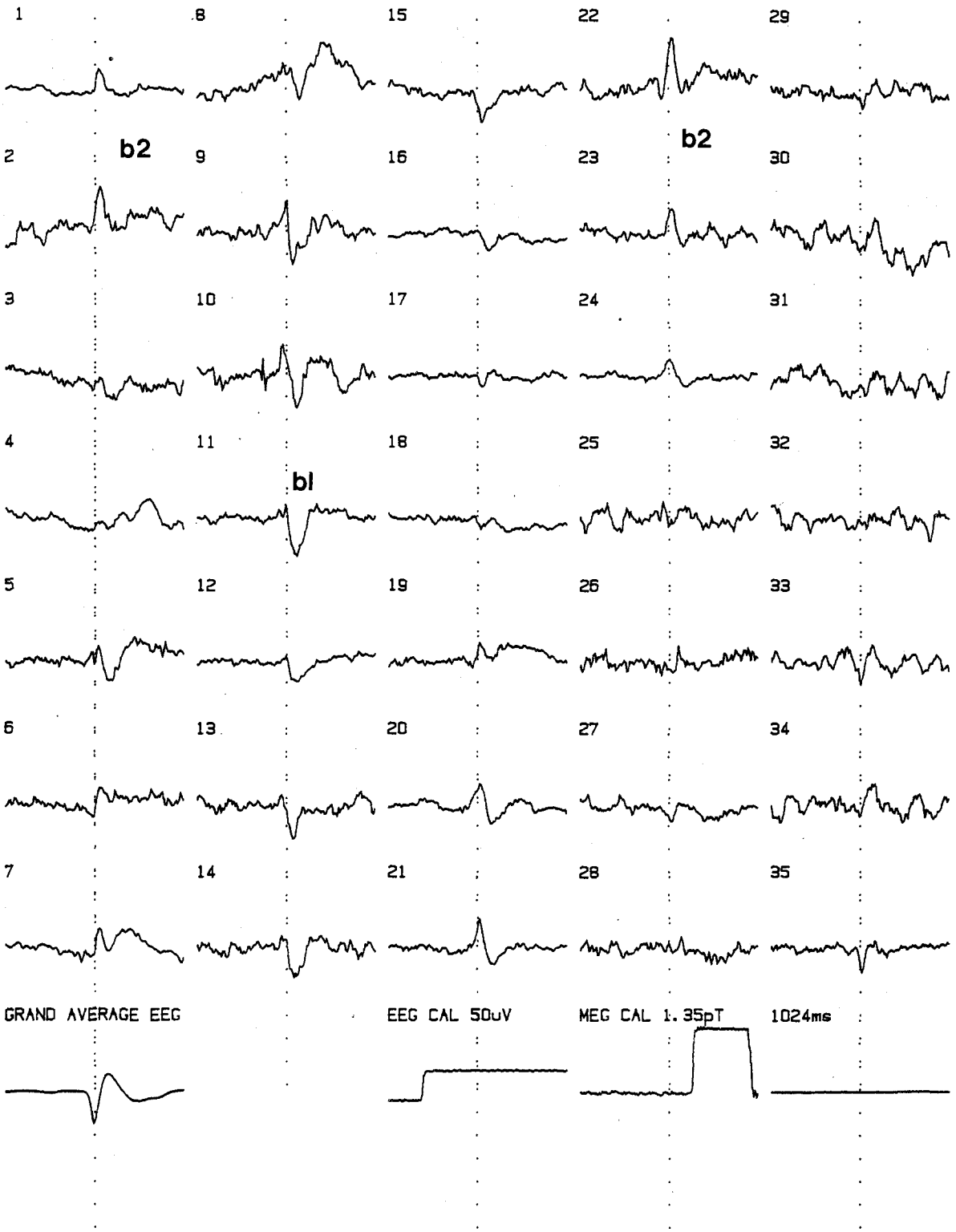

Fig. 7 A. The upward direction in the MEG plots represents fields entering the head.

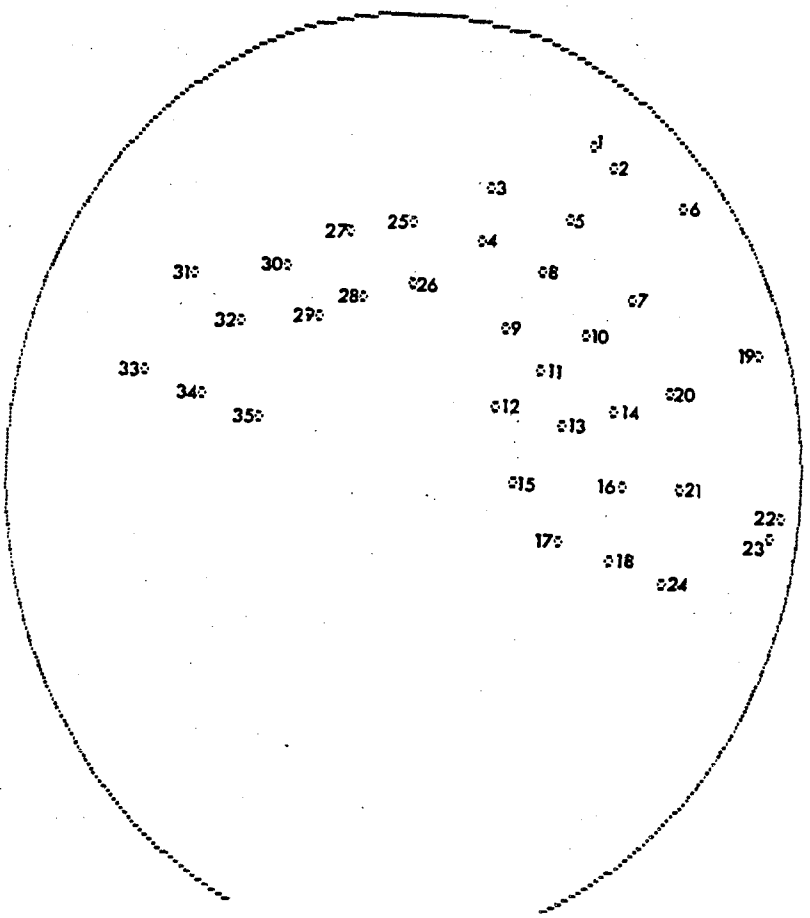
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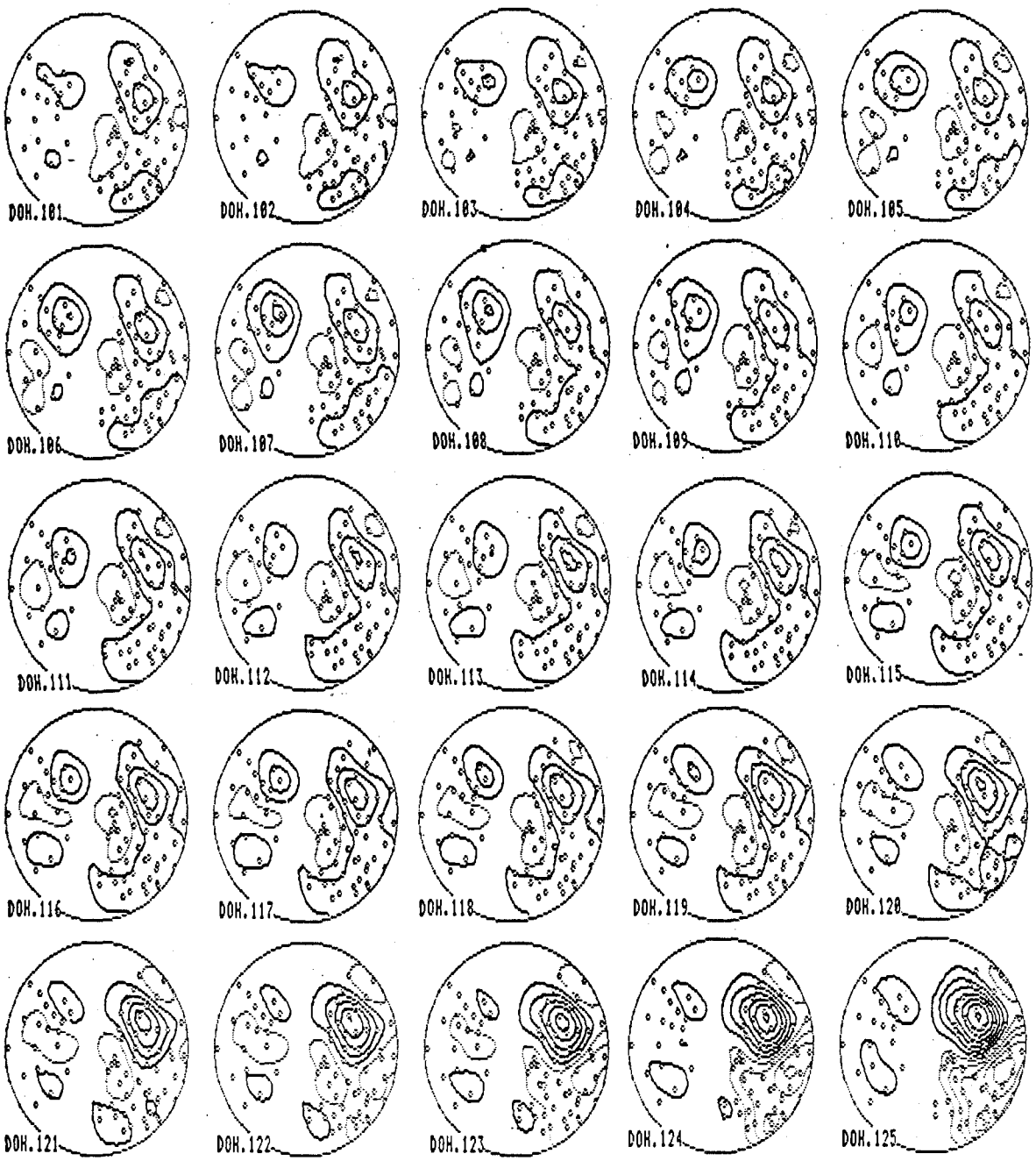
Fig. 8 Series of interpolated field maps (subject DOH) from 400ms to 796ms. DOH.101 is equal to data at 400ms. Thereafter, each map represents data at 4ms intervals.

Each contour line is equal to 49 femto Tesla (.049 pico Tesla). Solid lines represent fields leaving the head, dashed lines represent fields entering the head.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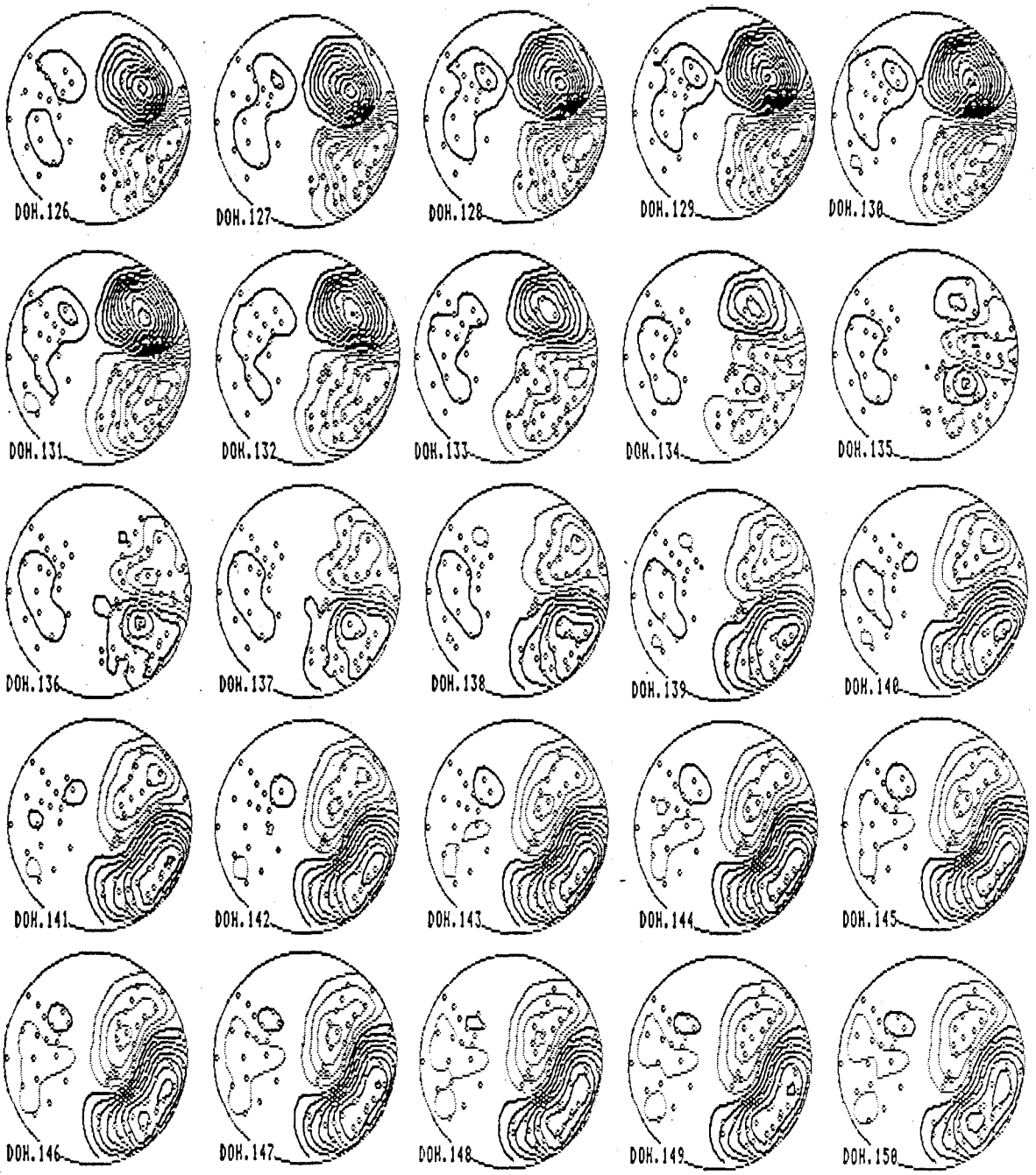
DOH.125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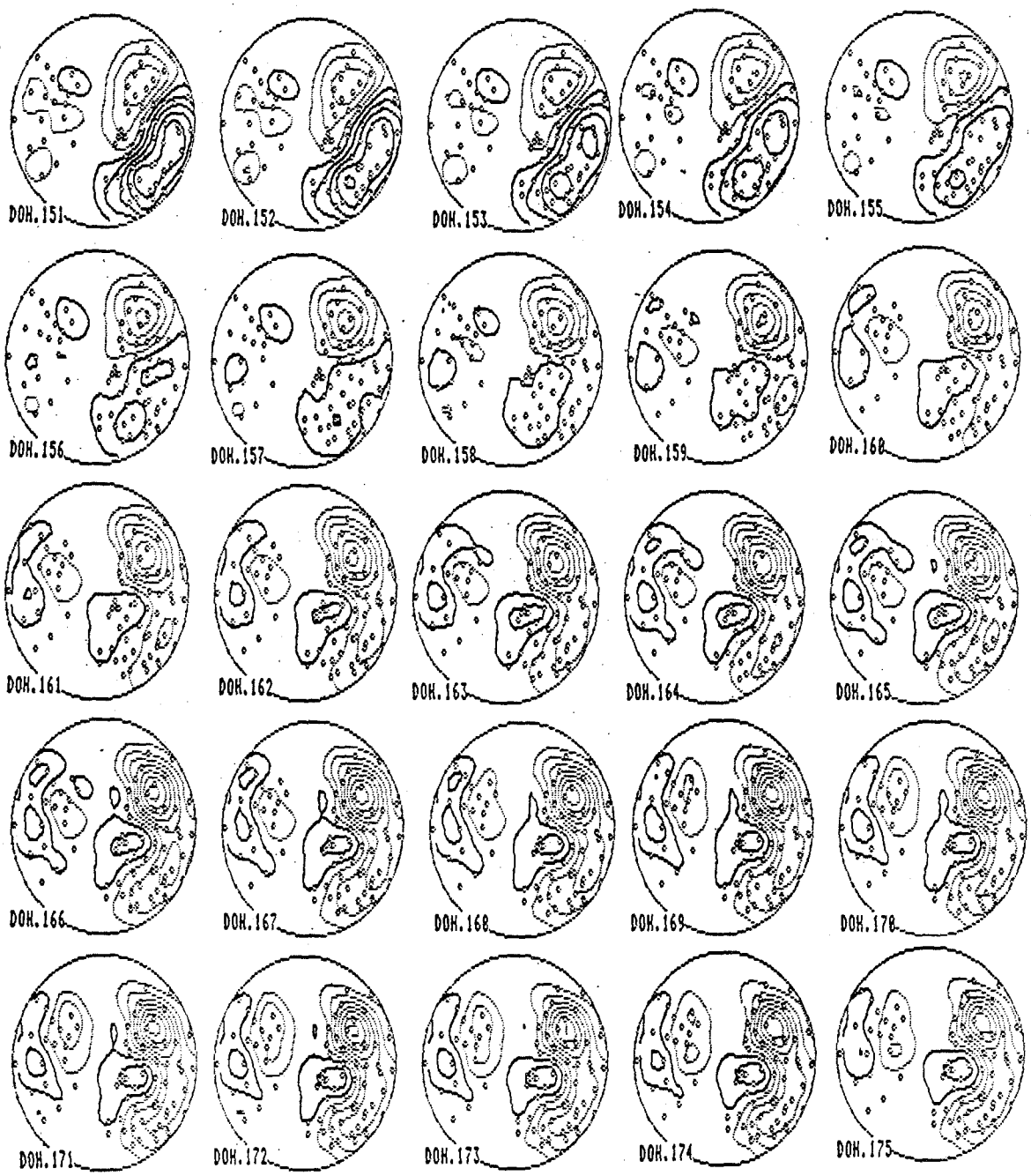
DOH.150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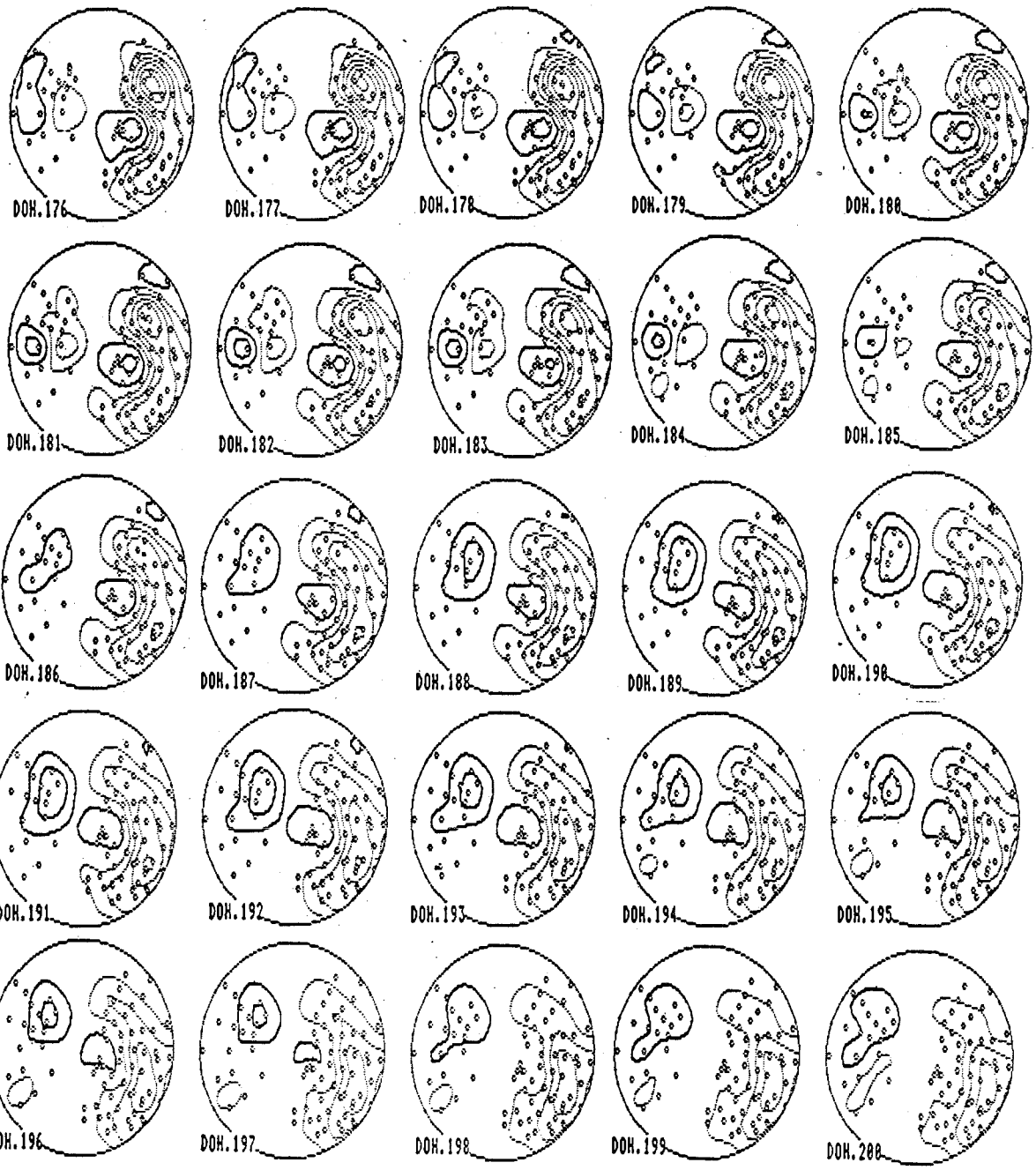
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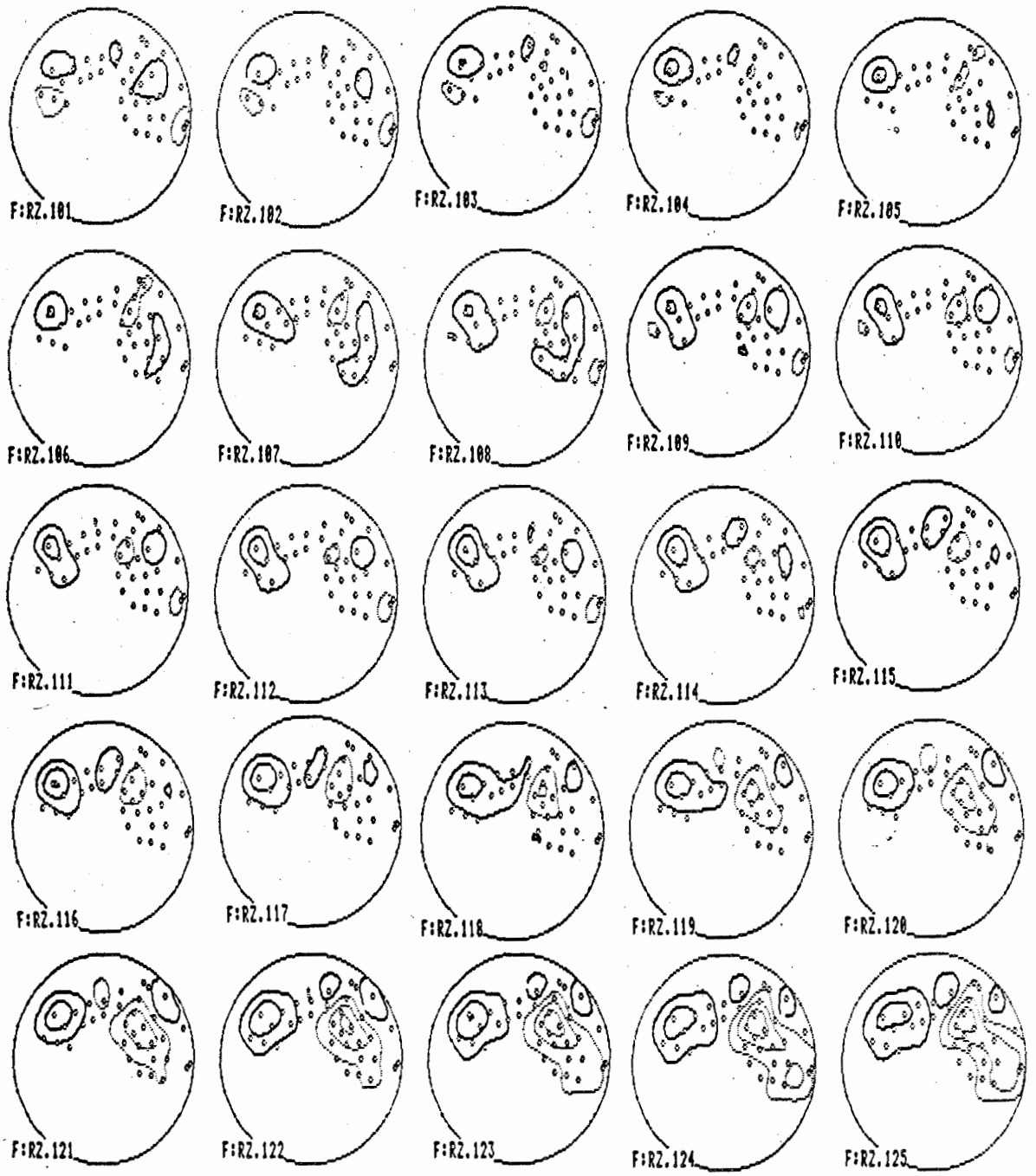
DOH.198
DOH.199
DOH.200

Fig. 9 Series of interpolated magnetic field maps (subject RZ) from 400ms to 796ms. RZ.101 is equal to 400ms with each map thereafter representing the data at 4ms intervals.

Each contour line is equal to 50 femto Tesla (.05 pico Tesla). Solid lines represent fields leaving the head, dashed lines represent fields entering the head.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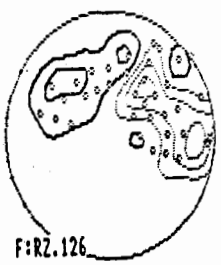
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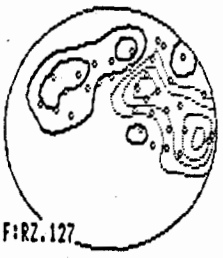
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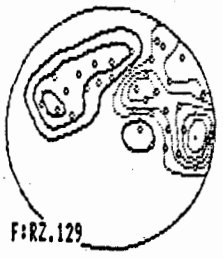
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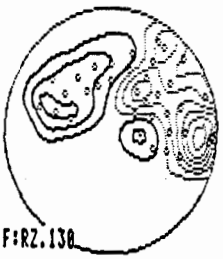
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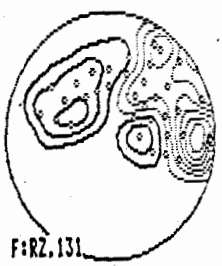
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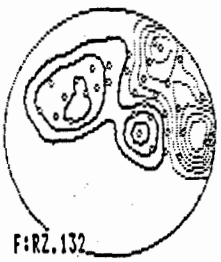
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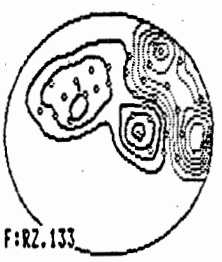
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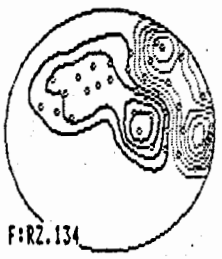
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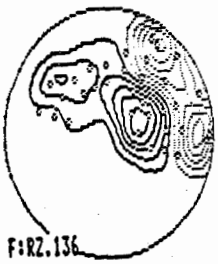
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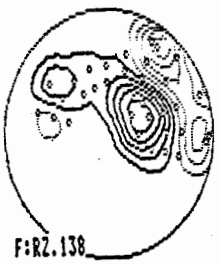
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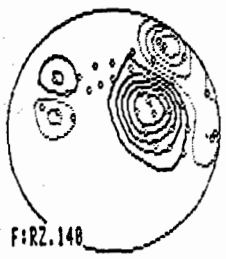
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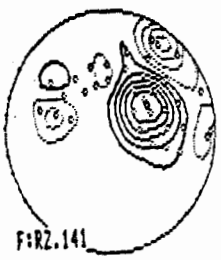
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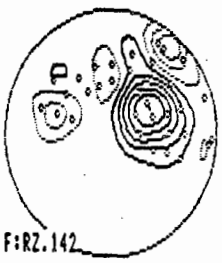
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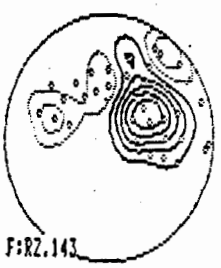
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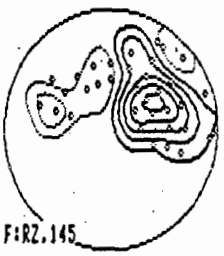
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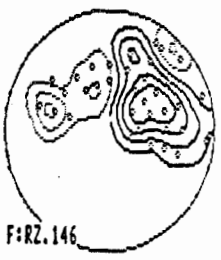
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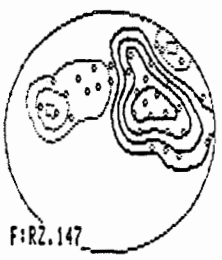
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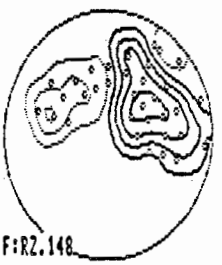
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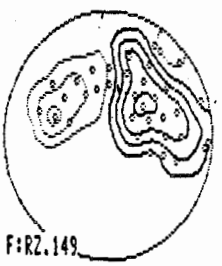
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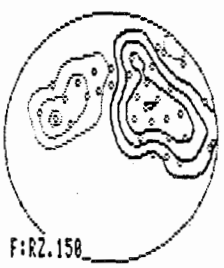
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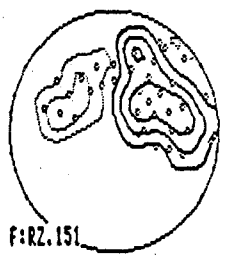
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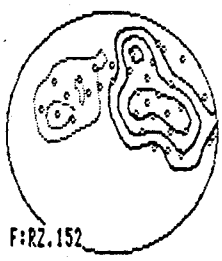
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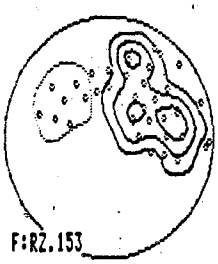
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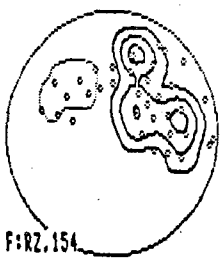
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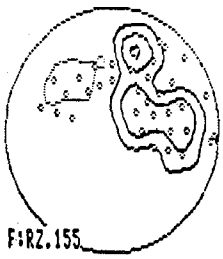
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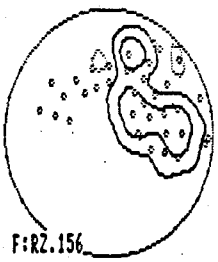
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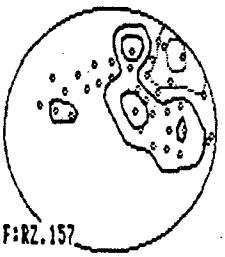
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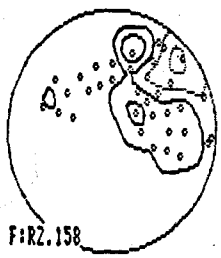
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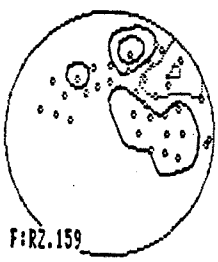
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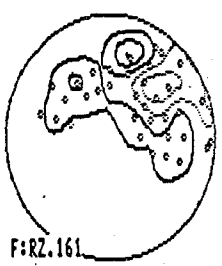
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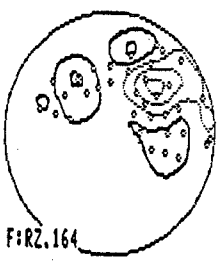
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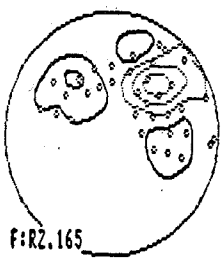
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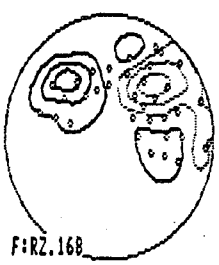
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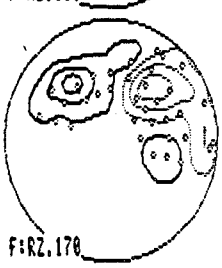
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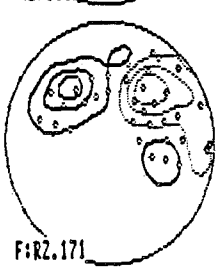
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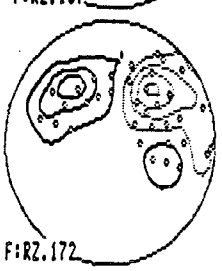
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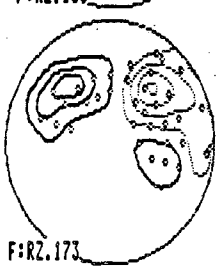
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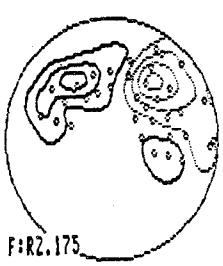
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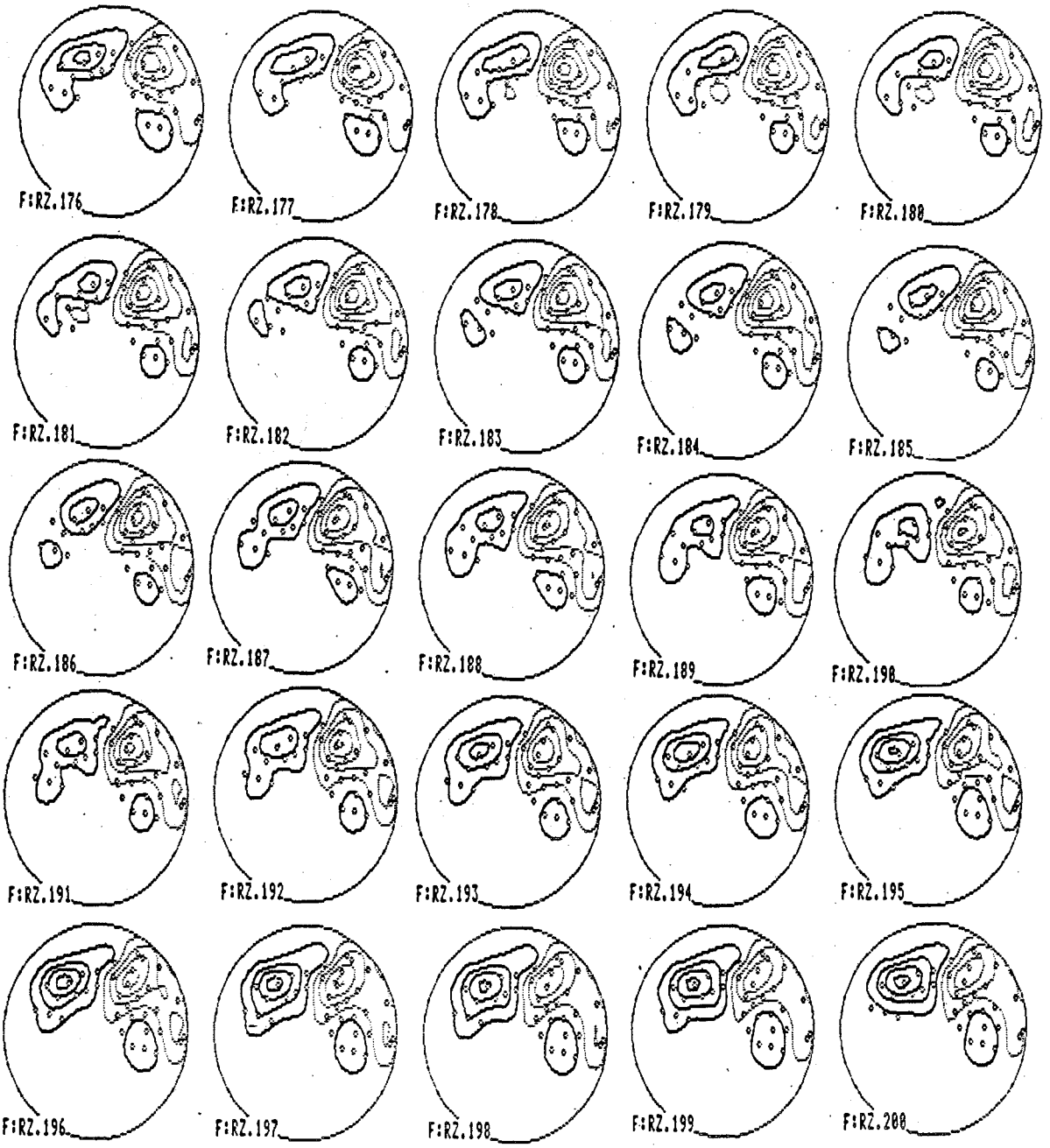
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Table I Results of dipole location estimation for DOH with respect to digitizer estimated origin.

Table II Results of dipole estimation for RZ. The first two estimates are simultaneous two-dipole fits. The second two estimates are single dipole fits to data selected on the basis of its dipolar distribution (see Fig. 4).

The X-axis is in the nasion to inion direction, nasion positive.
The Z-axis is in the vertical direction, vertex positive.
The Y-axis is in the left to right pre-auricular point direction, left positive.

The origin is determined by taking the midpoint between the pre-auricular points.

Single orthogonal dipole solution for data point DOH.129 (512ms)

Dipole parameters

Position			Orientation			Q(uV*m)
X	Y	Z	X	Y	Z	
.231	-3.790	1.494	.226	-.345	-.911	.5096E-05

% Variance accounted for=74

Single orthogonal dipole solution for data point DOH.144(572ms)

Dipole parameters

Positon			Orientation			Q(uV*m)
X	Y	Z	X	Y	Z	
-.059	-2.006	3.154	-.408	.774	.485	.1102E-05

% Variance accounted for=66

Table I

Two dipole solutions for data point RZ.135(536ms)

(1) Dipole parameters

Position			Orientation			Q(uV*m)
X	Y	Z	X	Y	Z	
-3.121	4.126	7.935	-.534	-.818	.215	.762E-05
-.212	.165	2.576	.904	.425	.047	.680E-05

% Variance accounted for=70

(2) Dipole parameters

Position			Orientation			Q(uV*m)
X	Y	Z	X	Y	Z	
.084	-3.227	2.209	.992	-.052	-.114	.213E-05
6.810	-5.905	11.70	-.570	-.817	-.081	.217E-05

% Variance accounted for=68

Single orthogonal dipole solution for data point RZ.135(536ms)

Anterior

Dipole parameters

Position			Orientation			Q(uV*m)
X	Y	Z	X	Y	Z	
2.545	-3.99	2.519	.741	.626	.245	.320E-05

% Variance accounted for=89

Posterior

Dipole parameters

Position			Orientation			Q(uV*m)
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-.313	-2.66	2.172	.837	.401	-.372	.136E-05

% Variance accounted for=58

Table II

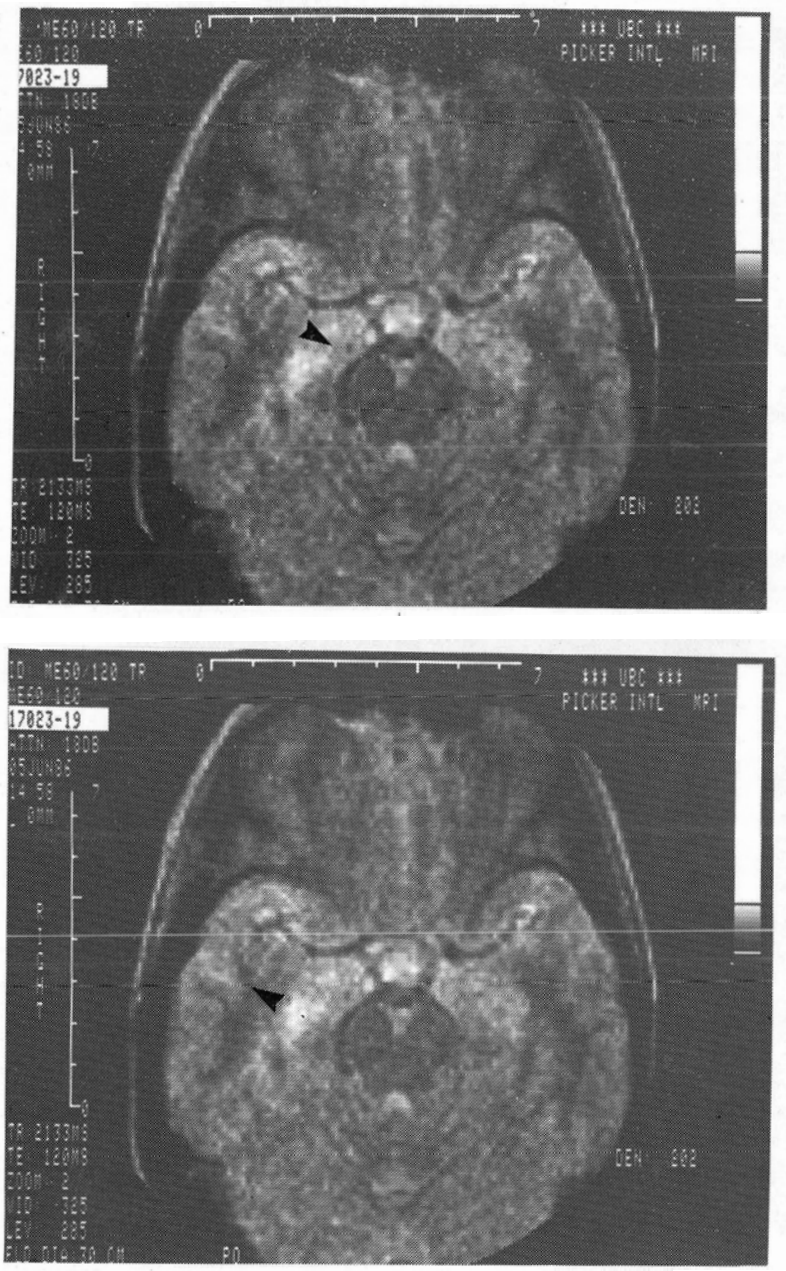

Fig. 10 Magnetic Resonance Image with dipoles indicated by arrows for subject DOH.
Top: dipole estimate for DOH.129
Bottom: dipole estimate for DOH.144
See Table I for details.

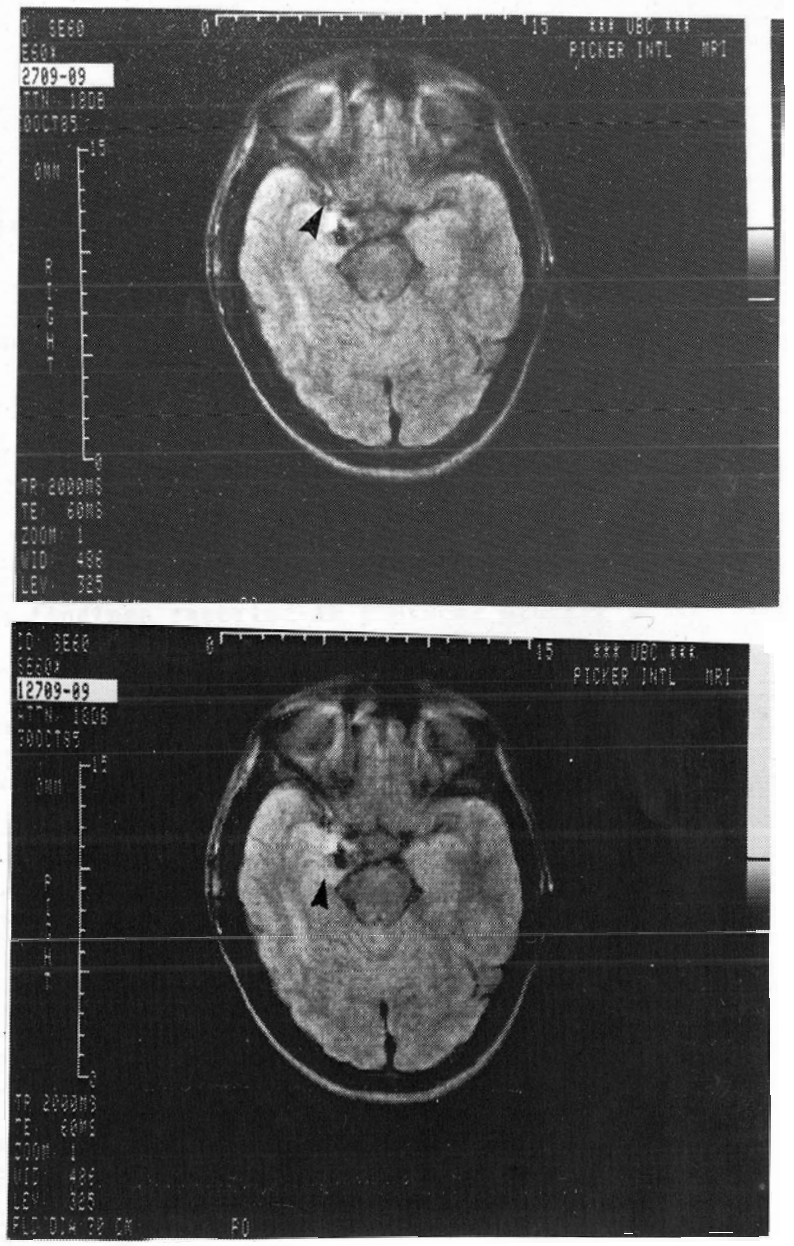

Fig 11 MRI with dipoles indicated for subject RZ.
Top: dipole fit for anterior selected data.
Bottom: dipole fit on posterior selected data.
See Table II for details, and Fig.4.

DISCUSSION

What is known about the electrophysiology of epilepsy is that in some cases the focus is localized, while in others the sources may be more distributed. The results indicate in general that the sources responsible for the discharges are much more localized for DOH than for RZ.

Subject DOH

MEG field patterns recorded over the right hemisphere of subject DOH are consistent with findings reported in previous studies of MEG in partial epilepsy (Barth et al., 1982; Barth et al., 1984). There is a clearly dipolar field over this hemisphere which shows the apparently characteristic inversion related to the positive peak of the EEG spike complex. For the right hemisphere, 3-d location estimation shows that the MEG can be an extremely useful tool for locating interictal epileptiform activity in the brain. Of particular interest in this subject, however, is the absence of left hemisphere MEG activity associated with the left sided EEG discharges. There is one other case of MEG associated with bilateral EEG spikes in the literature (Barth et al., 1982). In this case, the MEG detected bilateral dipolar fields, with a 20ms delay between them. Estimations of source location for each hemisphere, using the spherical assumption, showed locations which were approximately bilaterally symmetrical. This finding is consistent with the literature on the mirror focus (for a review see Mayersdorf Schmidt, 1982), which postulates that a cortical epileptogenic discharge in one hemisphere (the primary focus) may kindle a similar discharge in the homotopic area of the other hemisphere (secondary focus). In the case of a subcortical primary focus the secondary discharge may occur in synaptically related areas.

Although initially the secondary focus is dependent upon the discharge of the primary, it is theorized that over time the secondary focus may become independent. In the case of a mirror focus, one would expect to find souces of abnormality in both hemispheres. The absence of MEG spike activity over the left hemisphere of DOH suggests one of two possibilities: 1. that the EEG discharge is purely volume conducted activity with no functional tissue involvement on that side, or 2. that there is indeed functional involvement, but the source is oriented in such a direction that the MEG does not detect it. This could be the case if the dipole is radial. nowever, the second possibility raises the question of why, in one hemisphere, in this case the right, the source is not radially oriented, yet in the homologous area of the left hemisphere it is. There are three possibile explanations, the first being that there are asymmetries between the structures of the two hemispheres such that the tissues in the homologous regions in question are oriented differently; the second explanation being that present theories of mirror foci are partially incorrect, i.e., the mirror focus is not in the homologous region (M. D. Low, personal communication, 7th August, 1986). Most likely for this subject, however, is a third possibility, that the primary source is subcortical, as indicated by the MEG dipole localization and the MRI, and that the area is synaptically related, yet not necessarily homologous.

Given the different findings of Barth et al. (1982), and the present results, there is clearly a need for study of a large group of patients with bilateral discharges. Should additional cases of unilateral MEG findings be reported, neuromagnetometry might prove to be extremely useful in the differentiation of primary versus secondary electrical discharges.

Subject RZ

For subject RZ the data are more complex and indicate that there is no equivalent dipole which identifies the source of the discharge. However, this interpretation is important in two respects: (a) it suggests a more distributed and complex source in this patient, and (b) it illustrates, when taken in conjunction with the data of DOH, that current methods of source estimation are limited when multiple and distributed sources are involved. The application of the simplex procedure for the location of multiple sources at a time point when the maps were most dipolar resulted in clearly untenable locations. As a result, single dipole fits were determined separately for what appeared to be two sources (sharing a maximum) from an examination of the isocontour maps. The isocontour data at times following the EEG spike appeared to be more like that expected from a dipolar source. There are several hypotheses which could explain these data: 1. the sources are not dipolar, i.e., the spatial distribution is too great to be usefully described by a single equivalent dipole. 2. there are localized equivalent dipoles whose orientations are radial at the peak of the EEG spike. With current techniques radial dipoles cannot be detected by the MEG. The appearance of dipolar fields later in the epoch can be explained if the dipoles are non-stationary during the discharge and reorient to a position where the MEG can record their magnetic fields. The lack of field inversion so apparent in the data from DOH supports the hypothesis that the dipolar fields do not represent a simple delay in the detection of the fields related to the negative EEG component. Developments in the simplex algorithms are in progress which may allow the identification of non-orthogonal dipoles, i.e., dipoles which are not orthogonal to the orientation of the sensing coil of the SQUID. 3. there may be several dipolar sources which have been obscured by the averaging procedure. It may be of use to utilize the technique of discriminating EEG spikes of similar morphology for each position, and to either average together only

those spikes which are similar, or attempt single spike mapping as described by Sato et al. (1985).

CONCLUSIONS

Magnetoencephalography (MEG) is a non-invasive imaging technique which measures the magnetic fields associated with electrical activity of the brain. Because the magnetic fields are not influenced by the resistive properties of the cranium, and because the MEG measures intracellular currents, the technique may be used to localize the sources of brain activity accurately.

An important application of the technology is in the study of clinical disorders such as partial complex epilepsy. Not only does the MEG promise to benefit patients with the disorder, but PCE, in some cases,i.e., those with abnormal strucural images, offers the unique opportunity to verify the results of localization techniques.

This thesis has demonstrated some interesting findings, which in turn have raised some questions. Given the limited number of reported findings in the MEG-epilepsy literature, and given the fact that apparantly only those findings which fit the existing dipole location models are being reported, the exact usefulness of the procedure for this homogeneous disorder remains unknown. The results of the current work have added to the knowledge base. For DOH there is the entirely new finding of an electrical spike with no detectable associated MEG abnormality. For RZ, the activity recorded was very different from that contained in the literature. The field distribution and temporal sequencing are difficult to explain and suggest multiple and distributed sources which are different for different time intervals during the primary discharge (spike).

Unfortunately the seizure symptoms for these patients have not been

well documented clinically due to lack of witnesses to the seizures. Had they been well documented it would have been interesting to 'correlate' the MEG localization with behaviours thought to arise from those areas of the brain.

Although it has been argued that the subject with CPE offers an opportunity to use MRI in conjunction with MEG prcedures to validate the MEG findings, it is also recognized that not all people with CPE demonstrate structural abnormalities. In addition, sources of interictal spikes may not necessarily be at a site identical with that of the epileptogenic event. In part, this thesis was directed at investigating the usefulness of localizing sources of interictal discharges. The results indicate that the interictal discharge localization may prove to be useful. As a consequence of these findings it is postulated that MEG, once sufficient numbers of epileptics with structural abnormalities and/or depth EEGs have been tested, will offer a safe and accurate alternative to traditional localization techniques.

APPENDIX A: THEORETICAL CONSIDERATIONS IN THE INTERPRETATION OF THE MEG

NEURAL GENESIS OF THE MEG AND THE CURRENT DIPOLE

The goal of most biomagnetic studies is to determine the location of neural generators responsible for normal and pathological function of the brain. Simplifying assumptions are made in order to estimate the location, orientation and strength of currents responsible for magnetic fields. Most researchers use the model of a simple current dipole in an homogeneous sphere. Based on this model, and theory derived from empirical evidence, activities of particular cell groups are proposed to give rise to the biomagnetic fields observed. This appendix will describe this evidence and theory.

Physiological sources of neuromagnetic fields

Electrical activity of neurons can be described in terms of two major components, the slow graded potentials of synaptic transmission (synaptic potentials), and the rapid all-or-none potentials of axonal transmission (action potentials). Both types are the result of ion concentration changes across the cell membrane. These changes give rise to currents flowing within the intracellular structure in one direction as well as low density extracellular volume currents flowing in the opposite direction (Wikswo, 1983). Scalp-recorded electrical potentials recorded by the electroencephalogram (EEG) are believed to arise primarily from extracellular currents (Gabor, 1978). On the other hand, the dipole orientation for magnetic sources is in the direction of the intracellular currents, therefore, the magnetic fields sensed by the MEG are believed to arise primarily from intracellular current flow (Cohen & Hosaka, 1976). Experimental evidence which supports these conclusions comes from studies of isolated neurons (Swinney & Wikswo, 1981) where the intracellular

current clearly dominates the recorded magnetic field. The extracellular current contributes little because of its low density.

Intracellular currents arising from both action potentials and synaptic potentials could theoretically contribute to the magnetic fields, however, this is not believed to be the case for the following reasons: Action potentials are comprised of a negative potential associated with depolarization and a positive potential associated with repolarization. These occur within a very short interval, and in relation to the time resolution of the recording system can be considered to result in mutual cancellation. In addition, the rates of diminution of the two fields over unit distance are unequal. In the case of fields arising from synaptic activity, the graded fields should approximate a current dipole. Furthermore, current dipoles are analogous to an electrostatic charge dipole, a positive and a negative point separated in space, the magnetic fields of which diminish as the inverse of the squared distance. In the case of action potentials, the fields would be more accurately modelled as a current quadrupole because both depolarization and repolarization are present on the same axon producing intracellular current flow in opposite directions very close in space (Tripp, 1981). For a quadrupole the magnetic fields diminish as the inverse cube of the distance (Roth, Woolsey & Wiksow Jr., 1985). Thus, the contribution of these quadrupole fields will be considerably smaller per unit distance from the source compared with those of a dipole field.

For the above reasons, the magnetic fields sensed by the MEG recording device are assumed to be the result of intracelluar currents produced by depolarization or hyperpolarization on the postsynaptic membrane. The characteristics of postsynaptic potentials (PSP's) and the region of the cell upon which the excitation or inhibition occurs will

determine the direction of the current flow and the strength of the magnetic field at a distance. An excitatory PSP arriving at a dendrite would result in the movement of positive ions across the cell membrane into the cell, causing the intracelluar current to flow away from the dendrite towards the cell body (see fig.12) in the direction of lower resistance. Low density extracellular currents flowing in the opposite direction will complete the loop. The reverse direction of current flow will occur in the case of an inhibitory PSP. Postsynaptic potentials may also impinge upon a cell body resulting in current flow toward the dendrite. In both situations, these intracellular currents can be represented as a current dipole (Gabor, 1978; Okada, 1983). Finally, PSP's arriving at the centre of the dendrite will cause current to flow in both directions, a situation more adequately represented by a quadrupole rather than a dipole model (Okada, 1983).

Neuron morphology provides an important contributory factor to the current dipole model. Cells which have a symmetrical radial configuration of dendrites form "closed fields" which produce no externally detectable magnetic fields since the currents will cancel. Those cells which have a single dendrite and a long axon form "open fields" which produce large magnetic fields detectable at a distance (Lorente de No, 1947, from Okada, 1983). Morphologically most neurons fall between these two extremes. It is estimated that dipolar configurations of activity detected by the MEG (and the EEG) must be the result of simultaneously active, closely spaced cells in parellel orientation. Magnetic fields consist of both radial and tangential components. MEG measurements are made in such a manner that the radial component of the magnetic field is selectively detected. If the head is assumed to be spherical, a current dipole normal to the surface (a radial dipole) produces no external magnetic field since the volume current is perturbed by tissue change boundaries such that the sources

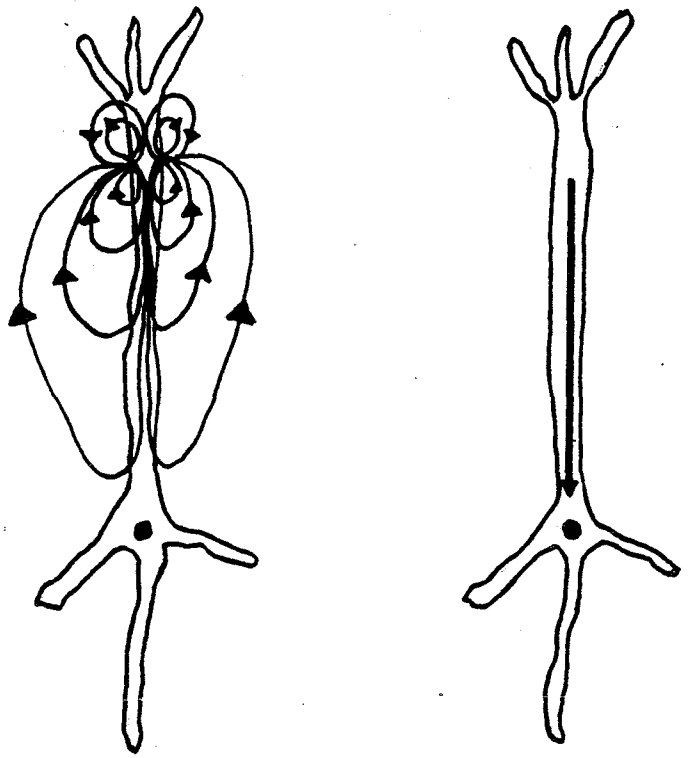

Fig. 12 Schematic representation of a pyramidal cell. A: Intracellular and extracellular current flow following depolarization on the apical dendrite. B: Intracellular current flowing away from the dendrite toward the cell body. This current can be represented as a current dipole.

from the perturbation just cancel the field from the current dipole. Only when the dipole is oriented tangentially will it produce a net external field (Williamson & Kaufman, 1981; Baule & McFee, 1965). Hence the cellular sources must be lying at an orientation tangential to the scalp. The cells which most adequately fit these morphology and orientation restrictions are the pyramidal cells, particularly those of the cortex which exhibit both columnar organization and appropriate morphology for the production of detectable magnetic fields. Due to the tangential orientation constraint, the dipoles are proposed to arise from pyramidal cells in the sulci rather than the gyri of the cortex (Okada, 1983). However, the spherical assumption is critical, as is the assumption that recordings taken normal to the skull will result in the gradiometer being radial to the origin. If these assumptions are violated the interpretations discussed above may be somewhat of an oversimplification. This issue will be discussed further in the following section.

Source estimation and the assumption of sphericity

Magnetic fields, as has been stated, consist of radial and tangential components. The current dipole model and assumption of sphericity, combined with a particular recording technique, theoretically give rise to selective detection of the radial component (Weinberg, Stroink & Katila, In press). The biomagnetic measurements are made with an instrument known as a gradiometer (see Appendix B for a complete description of the instrumentation). As the gradiometer is sequentially moved over a dipolar source it will detect magnetic fields emerging from one area of the head and reentering at another (the maxima and minima). At all times, the gradiometer is kept at an angle normal to the skull surface, which should result in the radial component being selectively recorded by the MEG.

Tangential components arising from perturbation of volume currents at tissue change boundaries are thereby ignored. This simplifies the interpretation of the fields. As a further consequence of the recording procedure, a null-flux zone is recorded over the point of field direction reversal. At this point no flux from the radial component of the field enters the ring which results in a null region. The distance separating the two extrema yields information regarding the depth of the dipole by the Biot-Savart Law (see Appendix B). The strength or moment of the dipole can then be estimated from the strength of the field and the estimated depth. The actual determination of location of sources based on recorded magnetic fields is an example of the "inverse problem" (Helmholtz, 1853, from Williamson & Kaufman, 1981b), there being no unique neuronal source configuration which would give rise to particular fields. Most researchers employ the simplified model of a current dipole in an homogeneous sphere with the dipole lying at the midpoint between the two extrema. Much neurophysiological evidence indicates that functionally meaningful generators of fields at the scalp are best thought of as equivalent dipoles. That is, the equivalent dipole represents the sum of a large active area with the equivalent dipole lying at the centre.

Although the skull is not spherical, and the tissue is not homogeneous, these assumptions have appeared to give reasonable accuracy for localization purposes. Further justification for the use of an homogeneous sphere model lies in the fact that concentric layers of differing resisitivities have no effect upon the normal component of the magnetic field outside the sphere (Grynspan & Geselowitz, from Pelizonne, 1985). Additional support comes from studies of sensory evoked magnetic fields. These studies show that experimental sensory stimulation produces field patterns with a dipolar distribution, and that estimates of source depth produce solutions which are physiologically reasonable (Kaufman,

Okada, Brenner & Williamson, 1981; Mclin, Okada, Kaufman & Williamson, 1983). Nevertheless, the spherical assumption has been shown by Ricci (1983) to prduce error. In addition, a recent report (Weinberg et al., 1986) in which dipoles were implanted in a skull, demonstrated that location estimates were more accurate when the true shape of the skull was considered.

If the assumption of sphericity is violated sufficiently, the gradiometer when normal to the skull surface will not necessarily be radial to the origin. This non-radial measurement will result in non-radial components of the magnetic field being recorded. This means that dipoles which are not tangentially oriented to the skull may contribute to the observed data. It is also possible that, under these conditions, there may be a contribution from volume currents (Weinberg, personal communication, 30th July, 1986). Although there has been no systematic attempt to record from non-tangential dipoles by deliberate manipulation of the gradiometer placement, Sutherling et al., 1985 postulated that distortion of fields observed over the cheek area of the face may have been due to non-radial measurement. The dipole localization program used in the present study is not dependent upon the gradiometer being radial to the origin.

APPENDIX B: INSTRUMENTATION

INTRODUCTION

The recording of electrical potentials of the brain has played a substantial role in clinical diagnosis and research for many years. Despite the usefulness of the technique however, its limitations have been well documented. It is well known that much information is lost due to tissues and fluids intervening between the sources of brain activity and scalp electrodes (Abraham & Ajmone Marsan, 1958), and that subcortical and cortical recordings are obviously, except in a few cases, not possible. Alternative techniques for accurate localization of cerebral sources of brain activity are being investigated. One which shows particular promise for a non-invasive technique is the magnetoencephalogram, the intstrumentation basis of which is the superconducting quantum interference device (SQUID).

1970 saw the introduction of the radio frequency (r.f.) SQUID (Clarke, 1986), a device which rapidly became commercially available, opening up areas of research and experimentation which would previously have been impossible outside low-temperature physics laboratories. The SQUID permits the recording of the tiny magnetic fields of the brain (and other organs), which unlike electrical potentials are not distorted by passage through the skull, scalp and dura.

This appendix focuses on the technology of the recording systems currently in use in biomagnetometry and, in particular, the instrumentation used for the collection of data for this thesis. Following a discussion of the superconducting quantum interference device and flux transporter is a description of the methods by which a cryogenic environment is provided and sustained, and consideration of the development of gradiometers and their effects on recordings of sources of

brain activity. In the final section there is a brief outline of the automated gantry system currently in use at Simon Fraser University.

SQUID

The SQUID (Superconducting QUantum Interference Device) is the instrumentation basis for the detection of the small magnetic fields of the brain. In order to explain the principles involved it is necessary to describe the two major components of the device: 1.The superconducting ring, and 2. The Josephson junction.

1. The superconducting ring

Although the phenomena of decrease in resistance with decrease in temperature had been known for many years, superconductivity was discovered by Onnes in 1913. He reported that when the temperature of mercury was lowered to 4.2 degrees Kelvin it showed a sudden, and apparantly complete loss of resistance. This discovery had profound implications, for without resistance one may have an indefinitely flowing current. More important for many present day applications of superconductivity is its use for the detection of extremely small signals, be they emanating from the brain or be they nuclear-spin noise (Clarke, 1986).

Superconductors are now generally made from niobium, which, like mercury, when lowered to temperatures near absolute zero (0 degrees Kelvin) also loses all resistance to current flow. Unlike mercury, the transition temperature (that temperature to which a particular material must be lowered to produce the state) is 9.2 degrees Kelvin (Zimmerman, 1983), a little higher than that for mercury. The superconducting ring

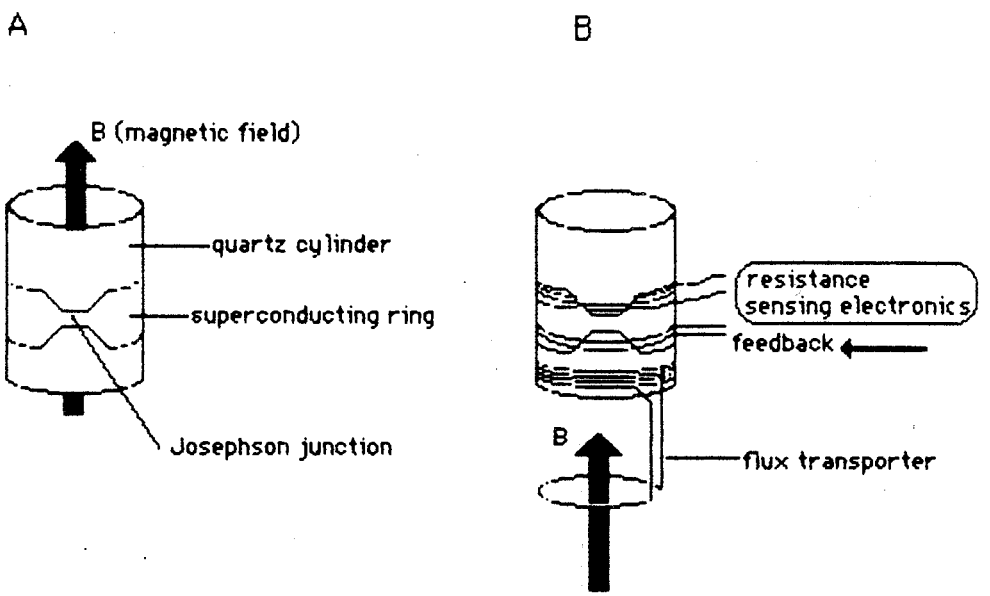

Fig. 13 Diagramatic representation of SQUID detection system.
A: Quartz cylinder with superconducting ring and Josephson junction.
B: Shows the relationship between the ring and the flux transporter, and the negative feedback electronics.

Adapted from Kaufman & Williamson, 1980.

is manufactured by deposition of a film of niobium onto a quartz cylinder (Clarke, 1986) (Figure 13a)

Long after the discovery of superconductivity Bardeen, Cooper and Shrieffer (1957, from Erne, 1983a), developed a theory of the superconducting state. They postulated that at very low temperatures a weak attraction force between electrons binds them together in pairs. In this state, unlike the normal-temperature state, the electrons cooperate. In a material at normal temperature, electrons behave randomly with respect to one another, but in the paired state of low temperature the electrons behave non-randomly with respect to one another. An important feature of the electron cooperation is that the electrons all respond similarly to an applied flux by showing wave-like properties through the superconducting ring. For reasons which will become clearer during the discussion of the Josephson junction, this wave function must meet at the same phase as it joins on itself around the circumference of a ring. The actual wavelength present at any time around the ring is determined by the total magnetic flux, phi, (field x area) within the circumference. The effect of external fields on the wavelength in the superconductor is the basis for its utility for the detection of tiny magnetic fields (Kaufman & Williamson,. 1980).

Cooling of a ring to produce superconduction is achieved by immersion in liquid helium which has a boiling point of 4.2 degrees Kelvin. The initial introduction of current into the superconducting ring can be achieved either during or after cooling. For purposes of this discussion it will be assumed that the introduction of current takes place during cooling. If, during the cooling process, a magnet is placed near to the ring the resulting quantized flux will remain trapped inside, and will be maintained by a current which flows on the inside surface of the ring.

Any magnetic field which is brought near to the ring after the initial current is set-up will induce a second, similar current, which flows on the outside surface layer of the ring. The second current is called a shielding current because its orthogonal magnetic field will oppose the introduction of further fields, as long as they are less than or equal to it. This opposition is known as the Meissner effect (Kaufman & Williamson, 1980). Should the applied field be larger than the opposing field, superconductivity will break down (S. Gygax, personal communication March 20, 1986).

Because the shielding current prevents the introduction of fields into the ring, even though the ring is extremely sensitive, those very signals in which a researcher is interested will go undetected by the device. Hence, the Meissner effect precludes the use of a simple superconducting ring as a device to detect magnetic fields. A relatively simple modification however, known as a Josephson junction, provides a device which has the advantage of high sensitivity provided by the basic ring, but circumvents the shielding effect.

2. The Josephson junction

The Josephson junction, basically a weak link in the ring, can be manufactured in a number of different ways (Weinberg, Stroink & Katila, In press), but is often produced by cutting away part of the ring at one point to leave a narrow bridge (Kaufman et al., 1980) (see Figure 13a). Once a Josephson junction is introduced to the superconducting ring, the application of magnetic flux effects the electron wave-function at the junction, thereby changing the electrical properties of the loop (Erne, 1983b). The characteristics of the weak link determine the critical current of the SQUID, that is, how much current can flow while the ring remains at zero resistance across the link (Kaufman et al., 1980). As the

shielding current passes through the link it becomes temporarily ineffective at opposing applied flux because it is of much lower value at the link than through the rest of the ring. This property allows magnetic flux to enter into the ring through the link in some multiple of flux quanta. Once the flux has entered the ring reverts to a superconducting state. The specifications of the link are often chosen such that one flux quantum (the flux quantum, phi nought, is the fundamental unit of flux equalling 2E-15 tesla per square metre) will enter the ring as it becomes temporarily normal (Romani, Williamson & Kaufman, 1982). A steady increase in the field causes the process to repeat periodically (Kaufman et al., 1980), in a step-wise linear manner.

A superconducting ring with a Josephson junction is known as a Superconducting Quantum Interference Device (SQUID). The radio frequency SQUID originally developed by Zimmerman (Weinberg et al., In press) consists of a ring with one weak link. In a direct current (d.c.) SQUID the ring has two weak links, the description of which is beyond the scope of this paper, except to say that it is a more sensitive instrument (Clake, 1986). Despite the fact that the d.c. type is not in common use it is gaining in popularity.

FLUX TRANSPORTER

The SQUID is not used to directly sense the magnetic fields because it must be surrounded by an insulating chamber (which will be described in more detail below), to isolate it from the biomagnetic and ambient fields. This shielding serves to prevent any fields from influencuing the SQUID except for those from a flux transporter (Figure 13b.). The flux transporter, also known as a flux transformer, is a detection coil made of

superconducting material which forms a closed circuit with the SQUID through an input coil. The size and geometry of the coils is chosen to maximize the signal-to-noise ratio based on information about biological sources and ambient noise (Kaufman & Williamson, 1980). A changing magnetic field imposed upon the detection coil induces an electric field and an associated current which flows to the input coil. At the site of the input coil the current establishes a magnetic field to which the SQUID responds. This combination of flux transporter and SQUID is known as a magnetometer. Electronic circuits, including a radio frequency circuit outside the SQUID, register the SQUID responses. By registration of these responses the circuits provide an output voltage proportional to the magnetic flux applied to the SQUID (Erne, 1983). Negative feedback cuurent, in proportion to the applied field, is provided by the monitoring circuits through a coil wrapped around the SQUID. The purpose of this feedback is to improve sensitivity by cancelling the effects of the applied field, thereby maintaing the total flux in the SQUID invariant (Kaufman et al., 1980; Romani et al., 1982).

CRYOGENICS AND DEWARS

One of the major problems in biomagnetics technology is the maintainence of temperatures sufficiently low to produce superconductivity. For the purpose of producing and maintaining low temperature SQUID sensing devices require a cryogenic environment, usually provided by immersion in liquid helium which has a boiling point of 4.2 degrees Kelvin (Kelvin is the Systeme International unit of absolute temperature, that temperature at which all thermal energy is removed). In the case of sensing devices the purpose of lowering temperature is to decrease the resistance of the sensing material. Resistance at normal

temperature is a function of thermal fluctuations of electrons within the material which present obstacles to current-carrying electrons (Zimmerman, 1983). In normal-temperature conduction these thermal fluctuations, also known as Nyquist noise, produce a voltage fluctuation which, in the case of a wire can be detected at its terminals. The thermal fluctuations are entirely random in nature and therefore carry no information other than temperature which is coded in their magnitude. Nyquist noise places a lower limit on sensitivity, because signals of smaller magnitude than the noise are undetectable. This problem can be circumvented with the use of cryogenically produced superconductivity. MEG in particular requires the greater sensitivity provided by superconduction, which is achieved by decreasing the kinetic energy, which in turn decreases the thermal fluctuations. In this state there is no resistance to the flow of current carrying electrons, and no noise to mask the minute signals.

The insulated chamber, usually made of fibreglass, which provides the cryogenic environment suitable for the SQUID, is called a dewar, the name of its inventor. It is basically a vacuum flask containing the helium in which the SQUID is immersed. Insulative material is mounted in the vacuum to prevent heat radiation, while vapor cooled shields absorb any heat and conduct it away from the coils, and eventually out of the dewar (Crum, 1985). Typically, the dewar contains 3 to 10 litres of helium which boils off over a few days so requires frequent filling. Closed system dewars are currently under development which can potentially alleviate the necessity for frequent refilling by trained personnel (Tward, 1985). As mentioned, the dewar not only provides the cryogenic environment, it also serves to shield the SQUID from all magnetic flux except that provided by the flux transporter.

GRADIOMETERS

Detection coils are capable of detecting very small magnetic fields, but they are not capable of discriminating them from background fields, and will respond to magnetic fields no matter what the distance from source. As a result, distant sources obscure fields from the brain. The major sources of interference include the earth's relatively large magnetic field which is approximately 70E-5 Tesla, as well as other sources common to urban environments, such as elevators, power lines and cars. The rejection of these ambient fields has presented a challenge which has been addressed by several different approaches: 1. isolation of the laboratory 2. shielding around the laboratory and, 3. use of the gradiometer in the recording system.

1. Isolation. Locating the laboratory in a rural, non-noisy environment has been the relatively successful approach taken by one group of researchers (Ricci et al, 1983). However, it is an impractical long-term solution for a technique for which there are hopes of a future significant clinical impact. Hospitals, with their heavy reliance on technology, present a particularly noisy environment.

2. Shielding. Shielding has been the approach of several investigators (Erne, 1983b). This also presents serious drawbacks. Some forms of shielding are extremely heavy and expensive (Sato, 1985), which limits their use. Other forms, which are less expensive, have performed well until necessary pieces of equipment such as visual stimulators are introduced to the environment, which defeats the purpose of the shielding.

3. Gradiometers. Explanation of the principles of gradiometers necessitates a brief account of the effects of magnetic fields on coils.

Changing magnetic fields produce electric fields which, in a conducting medium, will produce a current in a coil, a process termed induction. The induced current will in turn set up an opposing magnetic field within a coil. Gradiometers are constructed of a number of coils with a deliberately designed geometric configuration chosen to discrimiate between magnetic sources while maximizing sensitivity.

Gradiometers have proven to be the most practical tool for most neuromagnetic reseach groups. They measure the rate of change of the field as a function of distance from the source (Sato, 1985). In this approach the detection coil is supplemented by additional coils placed at distances appropriate for discrimination against unwanted sources. These parasitic coils are oppositely wound with respect to each other resulting in sensitivity to nearby biomagnetic sources and rejection of distant noise sources. The opposite winding is significant with respect to the intensity of magnetic fields over distance as the fields decrease as 1/r for the first order gradient, where r is the distance from the source to the detector. Thus nearby sources will produce fields which change rapidly over short distances, while fields from distant sources will decrease very much less over the same distance. As a consequence, very distant sources should produce the same flux in each coil, and since the coils are oppositely wound, a field producing a positive flux in one coil will produce a negative flux in the next, thus, they will cancel one another (Kaufman et al., 1980). Since their sources are distant, most ambient fields are relatively uniform. Fields from the brain, however, will diminish rapidly with distance from the scalp so producing differential flux at the first as compared with later coils (Romani et al., 1982).

Gradiometers can be 1st, 2nd or 3rd order. The simple detection coil

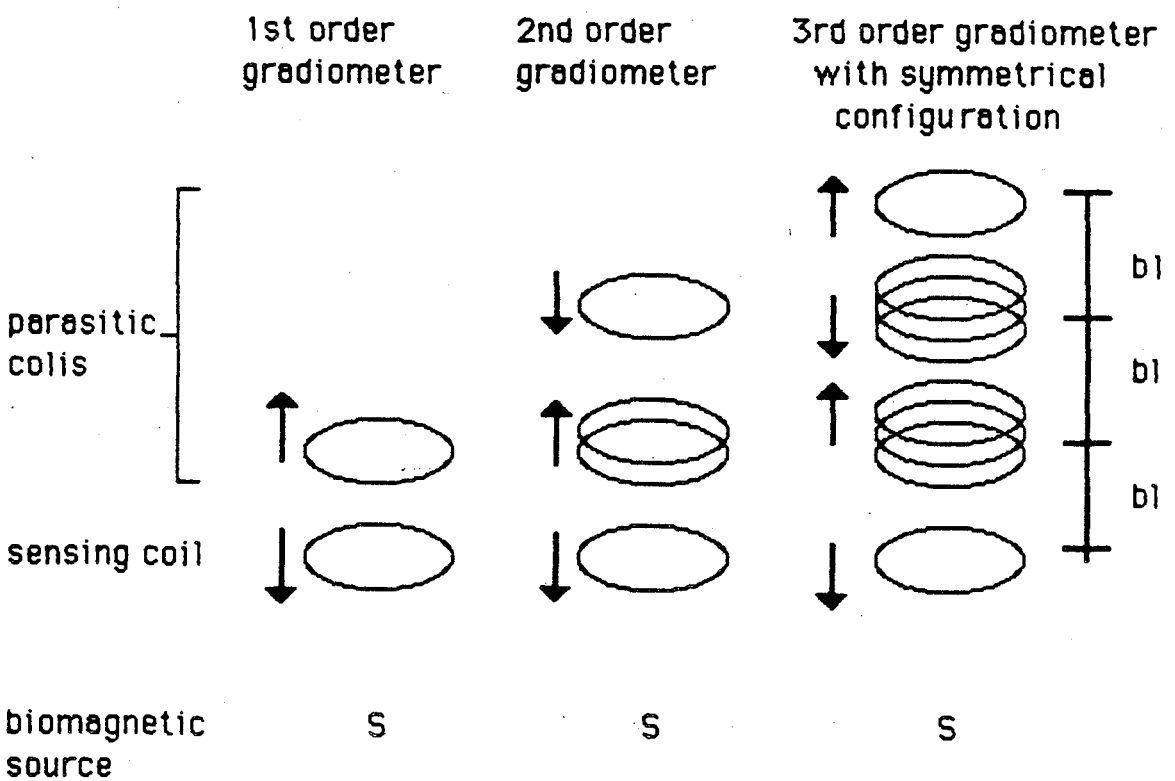

Fig. 14 1st, 2nd and 3rd order gradiometers. The arrow heads indicate the opposing direction of coil windings. bl is the baseline length between the parasitic coils. Modified from Vrba et al., 1982.

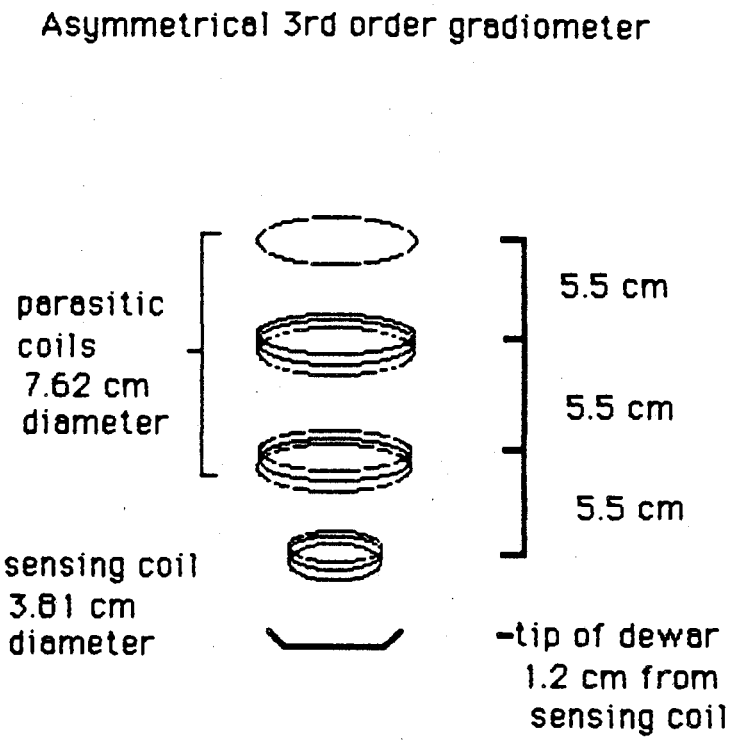

Fig. 15 Illustration of the asymmetrical 3rd order gradiometer currently in use at Simon Fraser University. Modified from Vrba et al.,1982.

is a magnetometer. A first order gradiometer consists of two magnetometers separated by a baseline distance and wound in opposite directions (Fig 14a), and can detect a spatial gradient of magnetic flux. Most biomagnetic laboratories use second order gradiometers which consist of two first order gradiometers connected in opposite orientations, separated by a second baseline distance (Fig 14b) (Vrba, Fife, Burbank, Weinberg & Brickett, 1982) which allows them to detect the second derivative of the spatial field gradient. The Brain Behaviour Laboratory at Simon Fraser University utilizes a third order gradiometer, a combination of two second order gradiometers connected in opposite orientation (Fig 14c). The third order device has been demonstrated to have superior noise rejection capability (Vrba et al., 1982).

There is, however, a cost for this improvement in rejection. Because the coils form part of the input circuit of the SQUID there is a decrease in the sensitivity of the SQUID system resulting from the detection coil sharing flux with more compensating coils (Carelli, Modena & Romani, 1983). It has been demonstrated that this loss in sensitivity in higher order gradiometers can be addressed by asymmetrical configuration of the coils (Vrba et al., 1982). In the asymmetrical configuration the parasitic coils are larger than the sensing coil. Because this results in a larger amount of flux in the parasitic coils the sensing coil is manufactured with multiple turns (Vrba et al, 1982) in order to provide equivalent area at the detection coil and parasitic coils. An illustration of the asymmetrically configured 3rd order gradiometer in use at Simon Fraser University is shown in Figure 15.

BASELINE LENGTH AND COIL DIAMETER

The introduction of a gradiometer into a recording system raises

important considerations in the estimation of sources. Indeed, the choice of various parameters must be based in large part upon the types of sources the researcher is intending to investigate. Reduction in sensitivity with higher order gradiometers has already disscussed, but there are other distortions which must be accounted for when attempts are made to localize underlying generators. In addition, the assumed source model dictates to some extent the accuracy of the final localization. In this case the model is the current dipole.

The current dipole is the most common source model assumed in neurophysiology. It is analogous to the charge dipole of electrostatics which has charge and length dimensions. Similarly, the current dipole model describes the movement of charge over a short distance (Kaufman et. al., 1980). In biomagnetic recording a dipole lying at depth d parallel to the scalp will show one position where the outward field is at a maximum, and a second position where the inward field is at a maximum, the two extrema. The Biot-Savart law can be used to describe the contribution to the magnetic field of current density in each infinitely small volume in space (Kaufman et al., 1980). The law shows that the distance (d) between the two extrema can be used to calculate the depth of the dipole, because the positions of most intense field directed inward and outward are displaced 2 d to either side of the dipole (Kaufman et al., 1981). The strength of the field is proportional to the maximum strength of the normal field at one extrema. Should the dipole be lying at an angle away from parallel the field strength will be reduced by the sine of the angle of tilt (Romani et al., 1982). Consequently, both the distance between the extrema and the apparent strength of the field are crucial for the determination of the actual depth and strength of the dipole. Choices of baseline length and coil diameter will be reflected in the data recorded by the system.

AUTOMATED GANTRY SYSTEM

For accurate localisation of dipole sources it is essential that the experimenter know the exact recording position over the head. The laboratory at Simon Fraser University, in conjunction with Canadian Thin Films Corporation, has developed an automated gantry system (Vrba et al., 1985) which not only allows precise positioning of the gantry with respect to the subject's head, but also records the placement angles for use in the data mapping and dipole localization programs. Part of this system includes a head modelling routine. For each subject a computer head model is produced by 3 dimensional digitization of the head surface. The head model is then used to by the computer-controlled gantry system to position the dewar over pre-selected positions on the subject's head. Should the dewar position not be quite normal to the head surface at a particular point, which may occur if the position happens to coincide with areas of rapidly changing skull surface, options exist for manual adjustment of the normal angle. Information regarding the final angular placement of the dewar with respect to the head model is stored by the computer for each recording position. These angles are used in the mapping routine and the dipole localization software as an integral part of the data display and spatial estimation of sources.

CONCLUSION

With its high degree of sensitivity the development of the SQUID has opened up new areas of research and enhanced existing techniques. Without doubt the area is still in the early stages of development and there remain significant technological problems to be overcome. Rejection of

Generally, the introduction of a gradiometer into the system tends to decrease the observed distance between the extrema (Romani & Leoni, 1985). In particular, small baseline lengths have been reported to distort the distance, simulating a shallower, weaker source (Romani et al, 1982). That is, if the extrema are close one may interpret a shallow source, and the strength b of the field will be assumed weaker for a shallow source than for a deep source. A further effect of baseline length is that smaller baselines decrease sensitivity (Vrba et al., 1982). This phenomenon is a result of the greater flux similarity in coils at shorter separation distances than at larger distances, that is, more flux will cancel.

Coil diameter has its main impact upon the sensitivity and spatial resolution of the system. Coils of large diameter, large being defined as equal to or greater than the depth of the source, increase the sensitivity. Unfortunately, there is a concomittant increase in the recorded noise. A second disadvantage of a large coil diameter is the loss of spatial resolution which is a result of the averaging effects of a large coil (Erne, 1983a). Finally, a diameter larger than or equal to the depth of the source places the extrema further apart than the true dipole position would predict (Romani et al., 1982). Clearly there is a trade-off when making decisions about the coil diameter and baseline lengths. Corrections which consider both parameters must be part of any localization technique, and involve consideration of the interaction of several effects. The dipole localization program currently in used for the analysis in this study (Harrop et al, 1986) includes corrections for baseline length and coil diameter.

ambient noise for instance, although handled well by gradiometers, continues to pose problems. The resolution of these difficulties is recognized by all who use the technology as an area for continued investigation. Another major hurdle is in the realm of cryogenics. Helium is expensive, the dewar is large, and its present design limits the introduction of multi-channel systems, and the positioning of subjects for recording (the dewar has a maximum 45 degree angle of tilt). Again, these limitations are recognized and work continues to eliminate the problems they pose. It may take several more years to find the solutions, yet the potential of the device as a research and clinical tool assures that the process is worth pursuing.

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